

# AKI in Neonates

## Epidemiology and Outcomes

David Askenazi MD, MSPH  
Professor of Pediatrics  
Director – Pediatric and Infant Center  
for Acute Nephrology (PICAN)



# Potential COI

- Speaker for Baxter, and the AKI Foundation
- Consultant for CHF Solutions



# Neonatal AKI

## Objectives

- Discuss the Scope of the problem
- Share lessons about neonatal AKI that you could potentially translate from the Crib-side to the Bed-side...



# Newborns

- **128 Millions** babies are born across the world every day
  - **17 million** in China
  - **4 million** in United States each year.
  - **5 million** in Europe each year.
- Most are either born at home, or in hospitals where they stay for a few days, then are sent home
- Some, however, are born without the ability to sustain life without support



# Sick Newborns

- In Europe

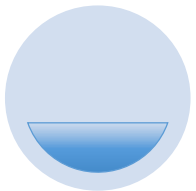
- ~80 NICU admissions per 1000 live birth
  - ~44 per 1000 for normal-birth-weight (2500-3999 g)
  - ~800 per 1000 for very low-birth-weight (<2500 g)
  - Epidemiologic Trends in Neonatal Intensive Care, 2007-2012 JAMA Pediatrics 2015

5.1 million live births \* (80 admission / 1000 births) =  
**410,000 babies a year are admitted to level 3 NICU**  
= 5% of all Intensive Care Admissions



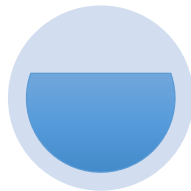
# Sick Newborns

- Some of these require some care (some dextrose, or warming, or supplemental oxygen for a few hours or days)
- Some of these require a bit more care....
  - IV fluids, IV antibiotics, Cardiac, nutritional, thermal, and ventilatory support
  - < 1% of NICU admissions receive Renal Support Therapy



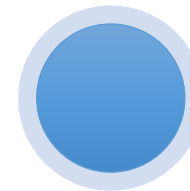
## VERY Premature Infants

- High Morbidity
- High Mortality
- Long LOS
- \$\$\$\$\$\$



## Premature infants

- Low Morbidity
- Low Mortality
- Moderate LOS
- \$\$\$



## Term infants

- High Morbidity
- High Mortality
- Mod / low LOS
- \$\$\$

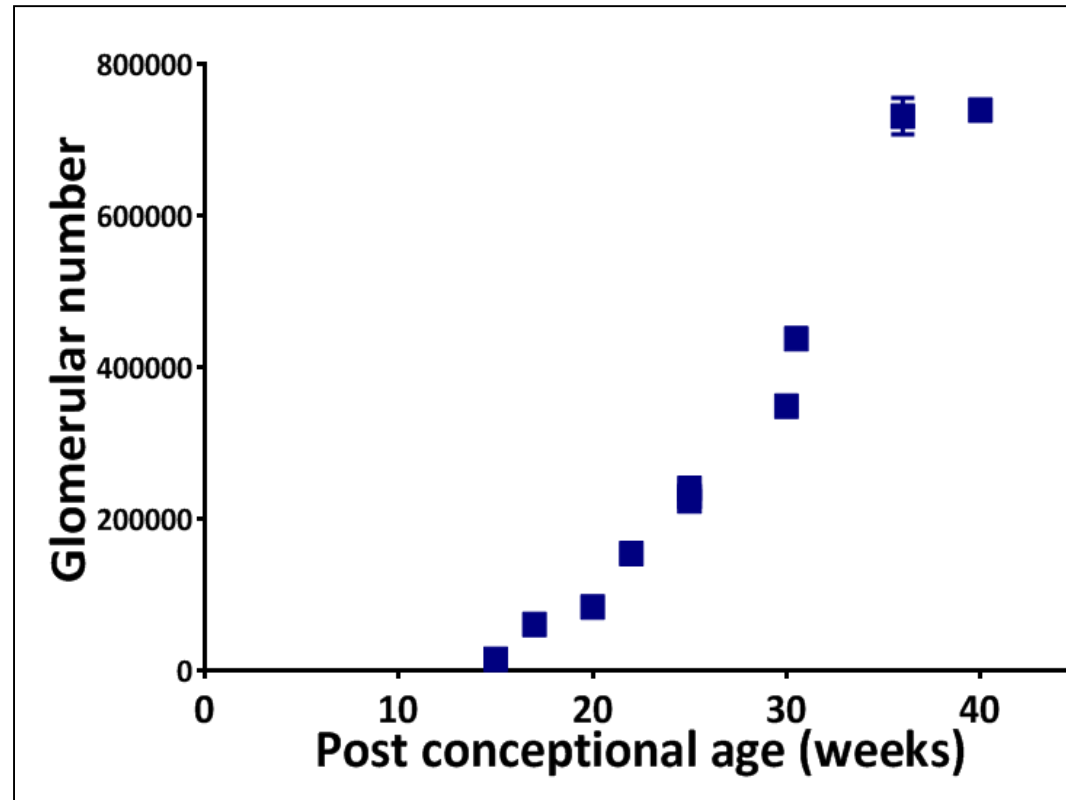
Nephrogenesis  
begins at 9  
weeks

Completed ~36  
weeks

60% occurs  
during the  
third trimester

Nephrons can't  
regenerate

## Preterm neonates



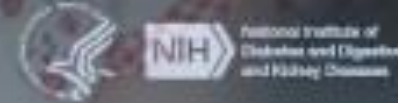
- Epidemiologic studies demonstrate an increase risk of CKD in those born <2.5 kg
- Of those enrolled CKiD 12% were born preterm.





# Neonatal Acute Kidney Injury Workshop

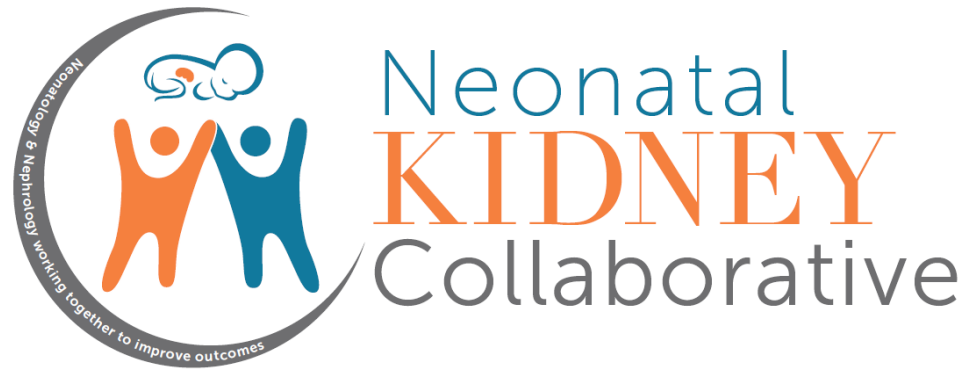
April 9, 2013



- Neonatal AKI workshop
  - Sponsored by the NIH NIDDK - April 2013
    - Marva Moxey Mimms MD - Program Officer at NIH
    - Multiple gaps in knowledge
    - Brought Neonatologist and Nephrologist together for the first time to begin work on this important topic







- Neonatal Kidney Collaborative
  - Short term goals:
    - Create Infrastructure for Communication Between Neonatology and Pediatric Nephrology
    - Use multi-center data to answer critical gaps in knowledge
  - Long-term goals
    - To improve the short and long-term outcomes for neonates at risk for kidney disease





# Neonatal KIDNEY Collaborative

The NKC includes at least one neonatologist  
and one nephrologist from 24 institutions  
4 countries: USA, Canada, Australia and India



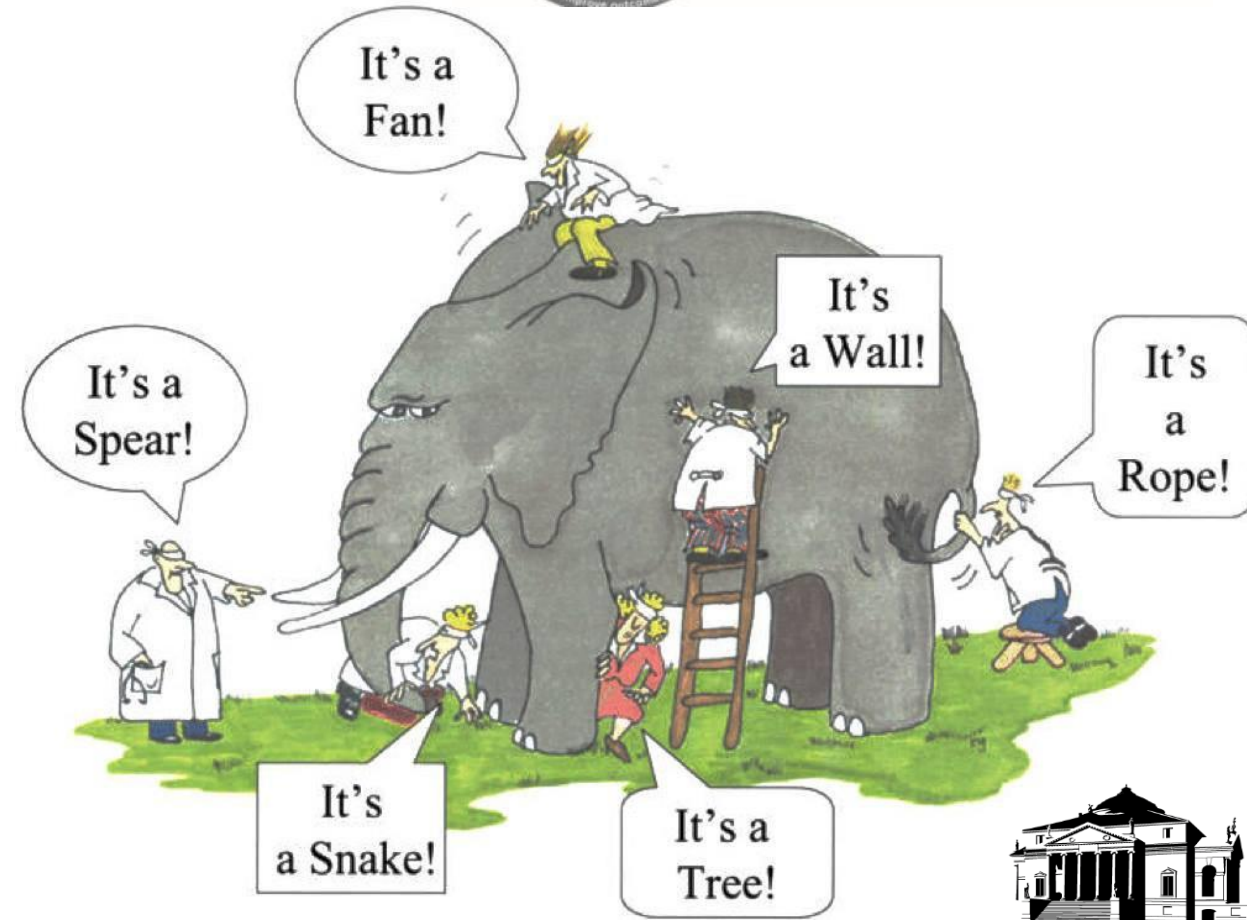
Thanks to all who are helping  
to AWAKEN the field of  
Neonatal AKI



Children's Hospital at Montefiore	Stony Brook University
University of Rochester	Children's National Med Center
University of Iowa	McGill University
University of Michigan	University of British Columbia
University of New Mexico	University of Virginia
University of Washington	Texas Children's Hospital
University of Alabama at BHM	Maimonides Medical Center
Cincinnati Children's Hospital	Canberra Hospital
University of Kentucky	The Medicity Hospital
University of Miami	Children's Hospital Colorado
Metrohealth Medical Center	St. Louis Children's
Nationwide Children's	Tufts - Boston

# Lesson # 1

- Develop Collaborations with really smart, people who are as passionate about the field as you are
- Important to look at an elephant from different perspectives
  - We PURPOSEFULLY have developed the entire collaborative on the basis of a partnership between Neonatology and Nephrology!
    - Committee leadership
    - Manuscripts
    - Definitions
    - Databases development
    - Mentorship





# What does this collaboration do?

- We have conducted a 24 center retrospective study “ AWAKEN “ which will help us answer many questions
  - As of May 2019
    - 9 papers published
    - 2 additional papers have been submitted for publication
    - 3 additional papers in preparation
- AWAKEN has provided preliminary data for a U34/U01 NIH funded study (ARISING)
- We have 4 arms to our mission
  - Research
  - Advocacy
  - Communication
  - Education



# AWAKEN

- Assessment
- Worldwide
- Acute
- Kidney
- Epidemiology
- Neonates



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

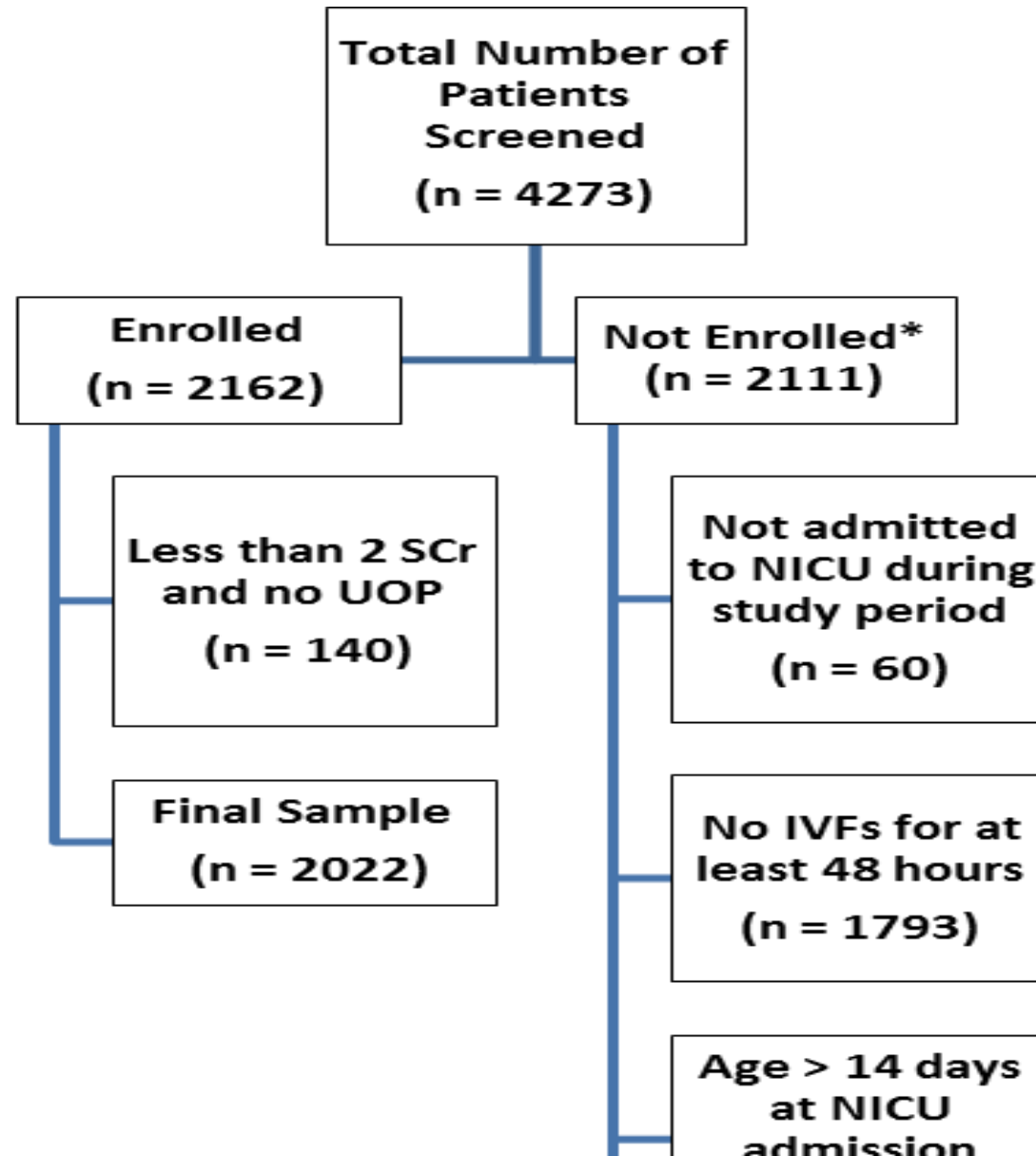


*Jennifer G Jetton, Louis J Boohaker, Sidharth K Sethi, Sanjay Wazir, Smriti Rohatgi, Danielle E Soranno, Aftab S Chishti, Robert Woroniecki, Cherry Mammen, Jonathan R Swanson, Shanthi Sridhar, Craig S Wong, Juan C Kupferman, Russell L Griffin, David J Askenazi, on behalf of the Neonatal Kidney Collaborative (NKC)\**

**Published on September 7<sup>th</sup>, 2017 – Lancet: Child and Adolescents - online first**



# AWAKEN: Breakdown of Screened vs. Enrolled    NICU admissions from Jan 1 – March 31, 2014



# Neonatal AKI definition

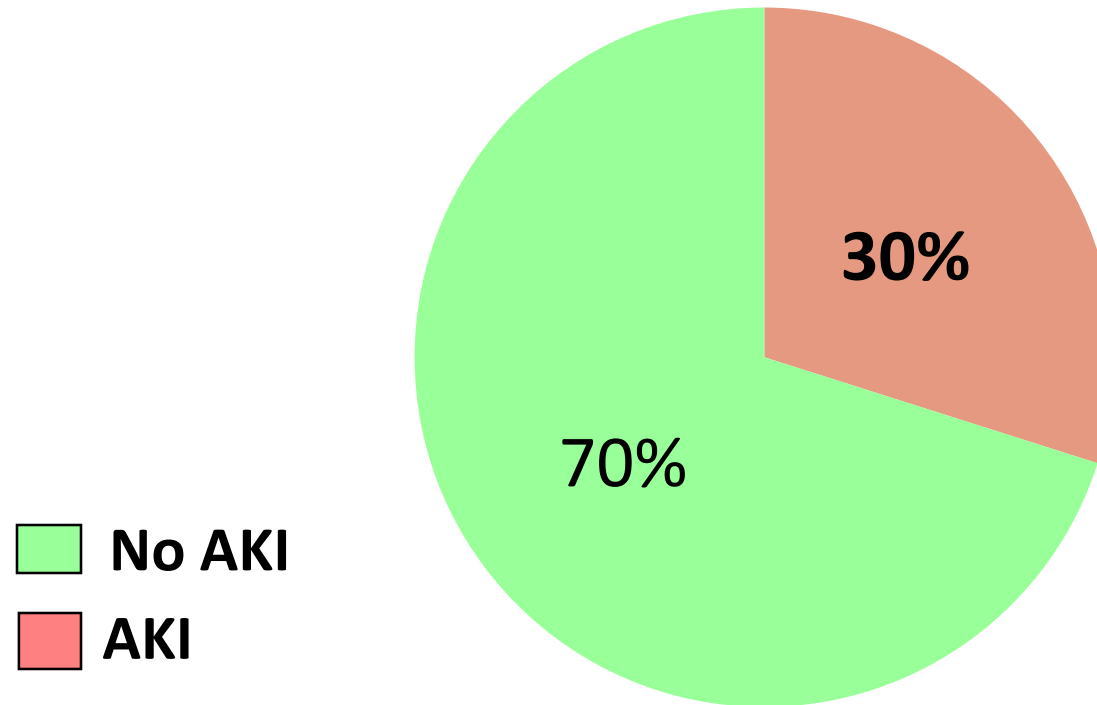
Stage	Serum Creatinine (SCr)	Urine Output (UOP)**
0	No change in SCr or rise < 0.3 mg/dL	> 1 ml/kg/hour
1	SCr rise $\geq$ 0.3 mg/dl within 48 hrs or SCr rise $\geq$ 1.5- 1.9 X reference SCr*	> 0.5 and $\leq$ 1 ml/kg/hour
2	SCr rise $\geq$ 2 to 2.9 X reference SCr*	> 0.3 and $\leq$ 0.5 ml/kg/hour
3	SCr rise $\geq$ 3 X reference SCr * or SCr $\geq$ 2.5 mg/dl or Receipt of dialysis	$\leq$ 0.3 ml/kg /hour

\*reference value is lowest previous value

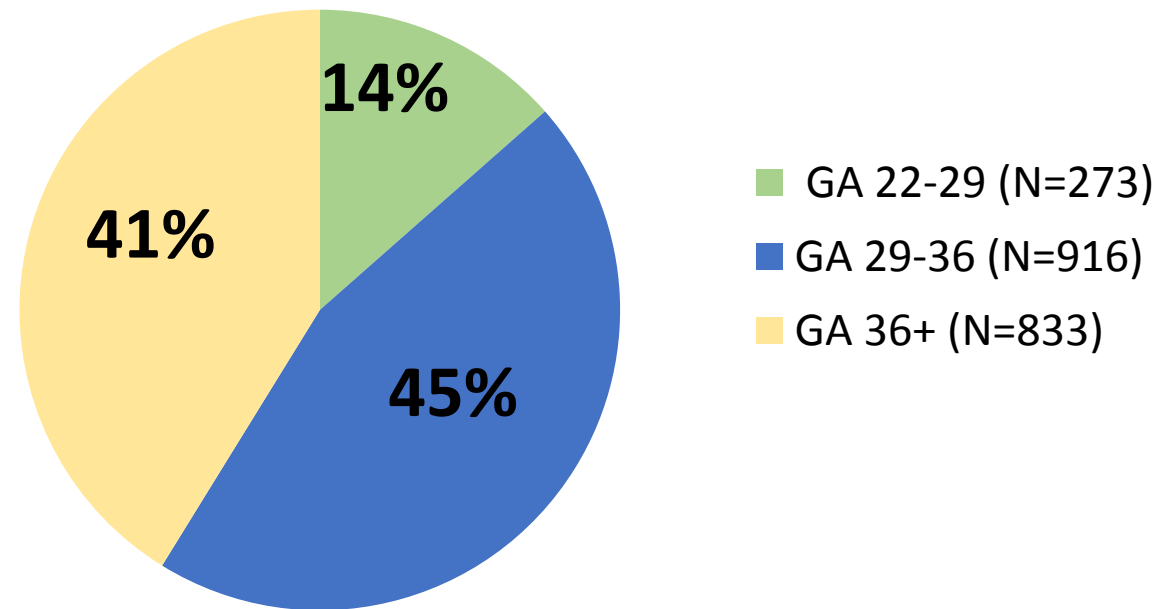
\*\*includes days #2-7 only (day of birth = day #1)

# AKI Incidence in AWAKEN study

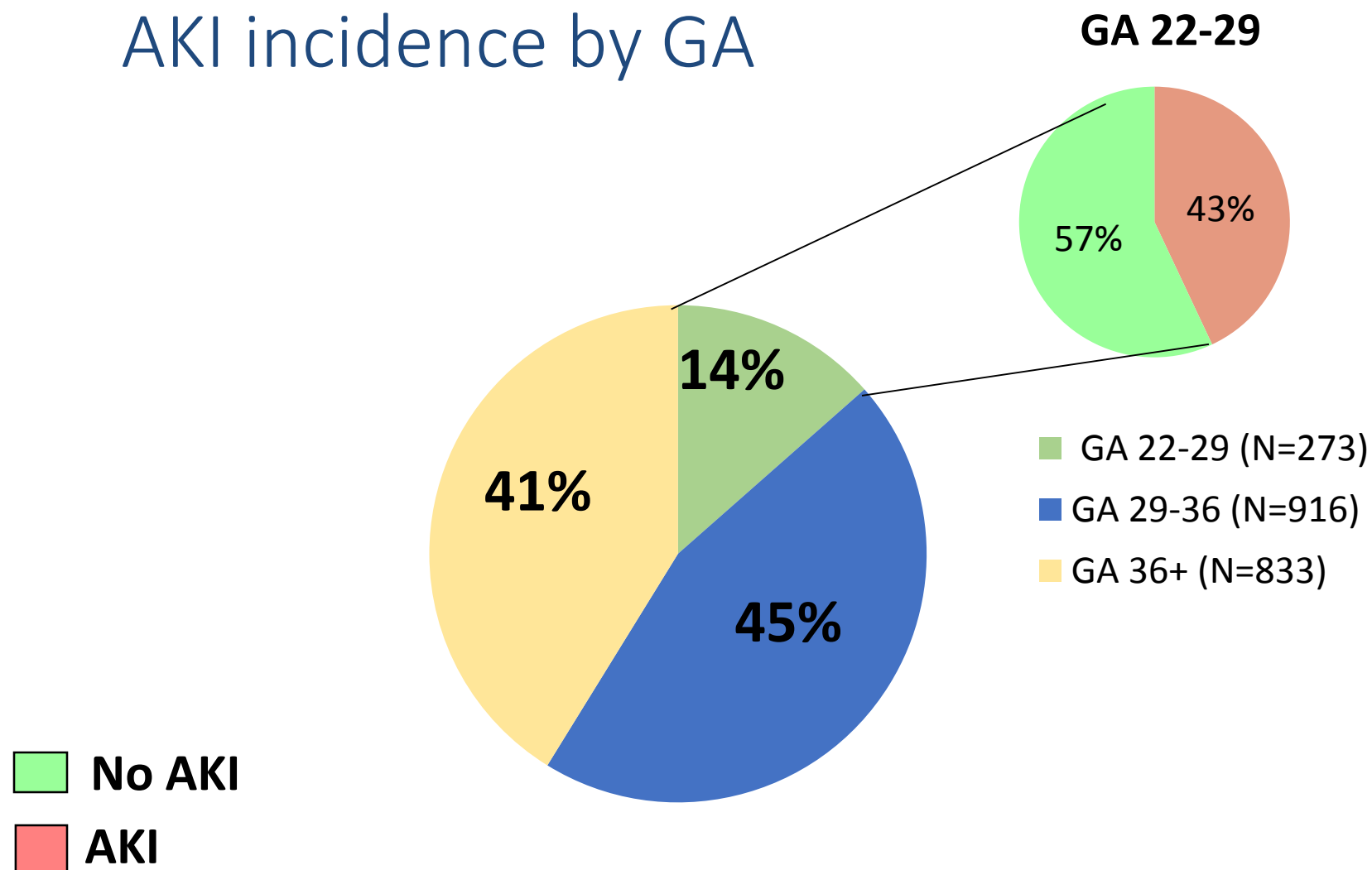
## All Enrolled Neonates



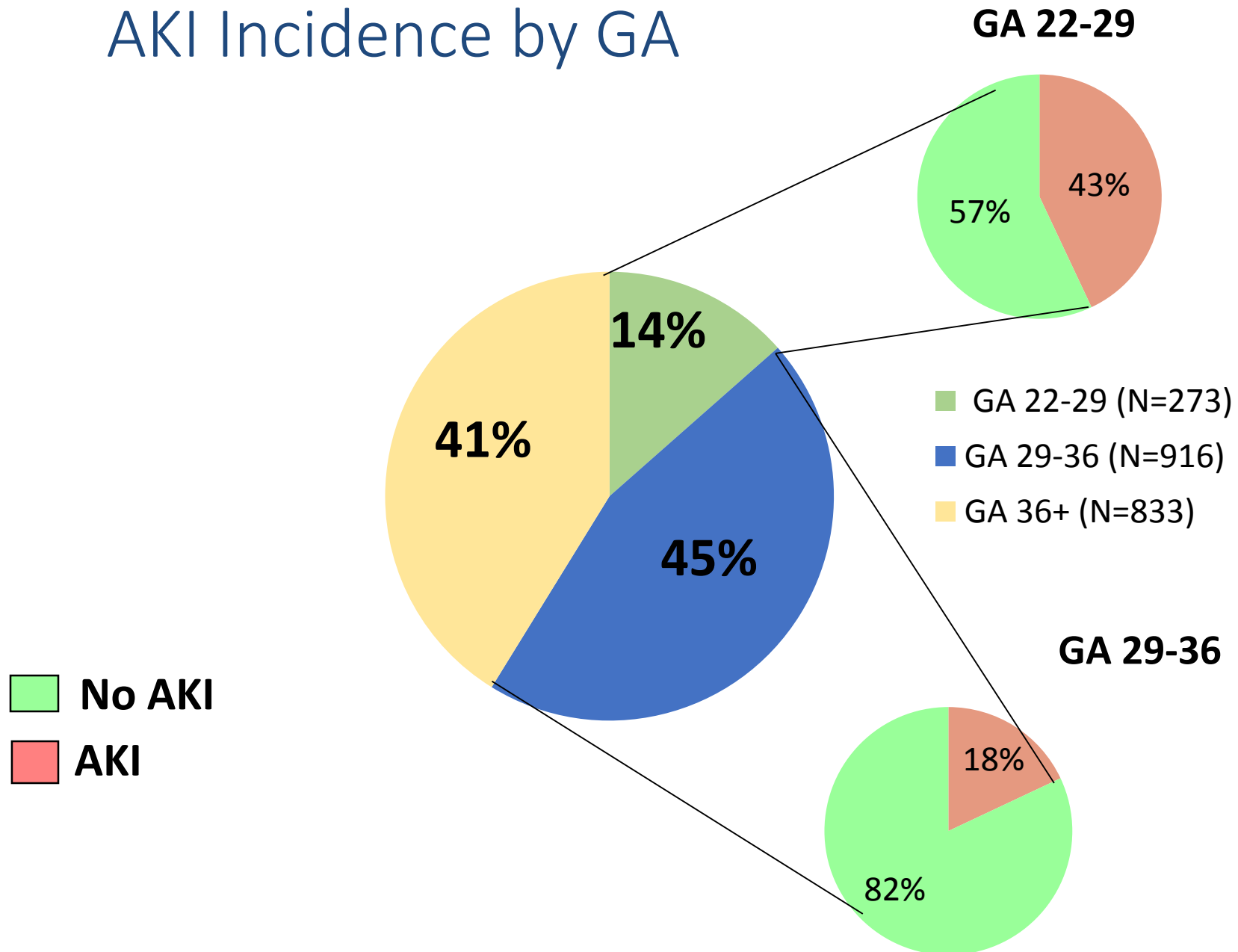
# AKI Incidence by GA



## AKI incidence by GA

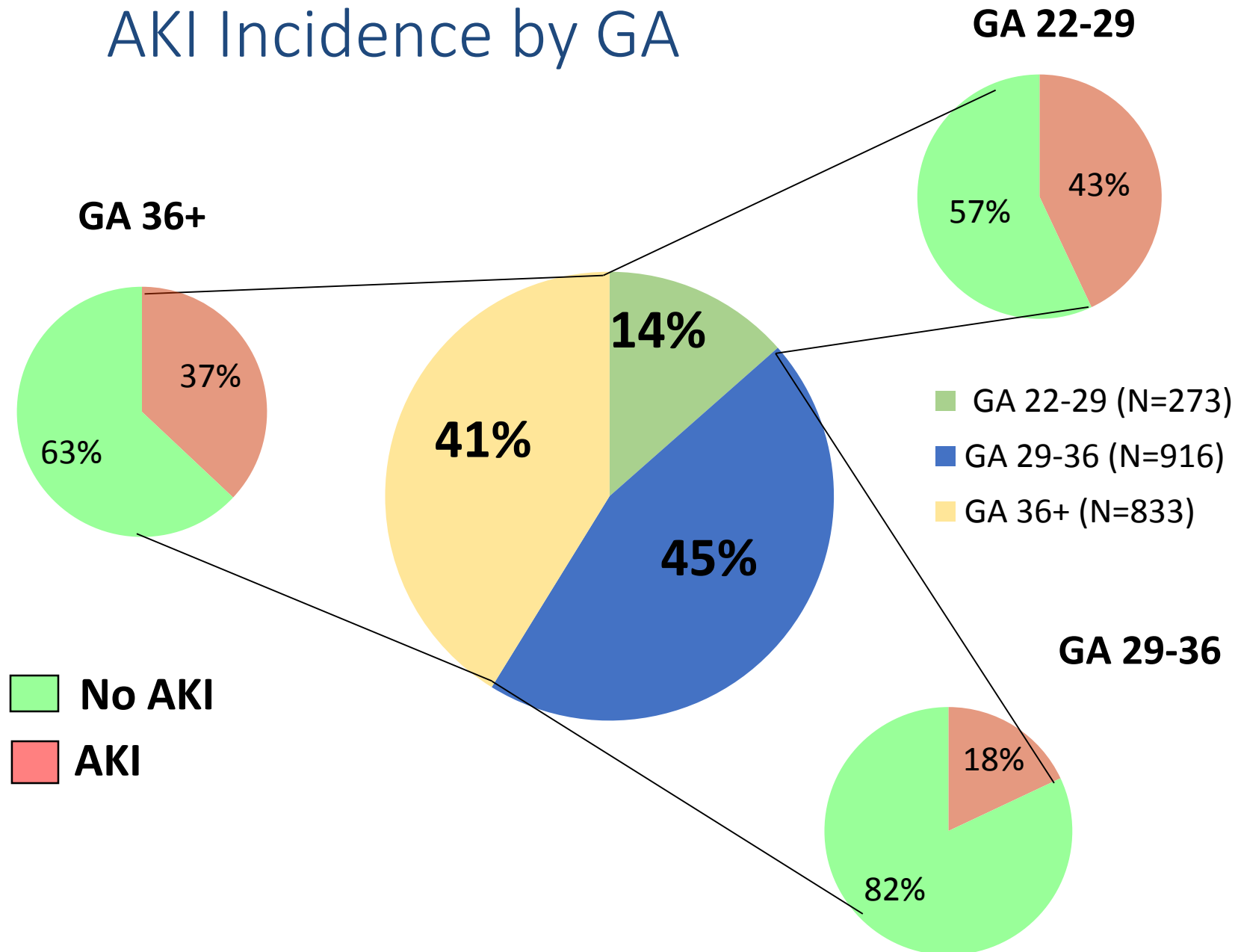


# AKI Incidence by GA





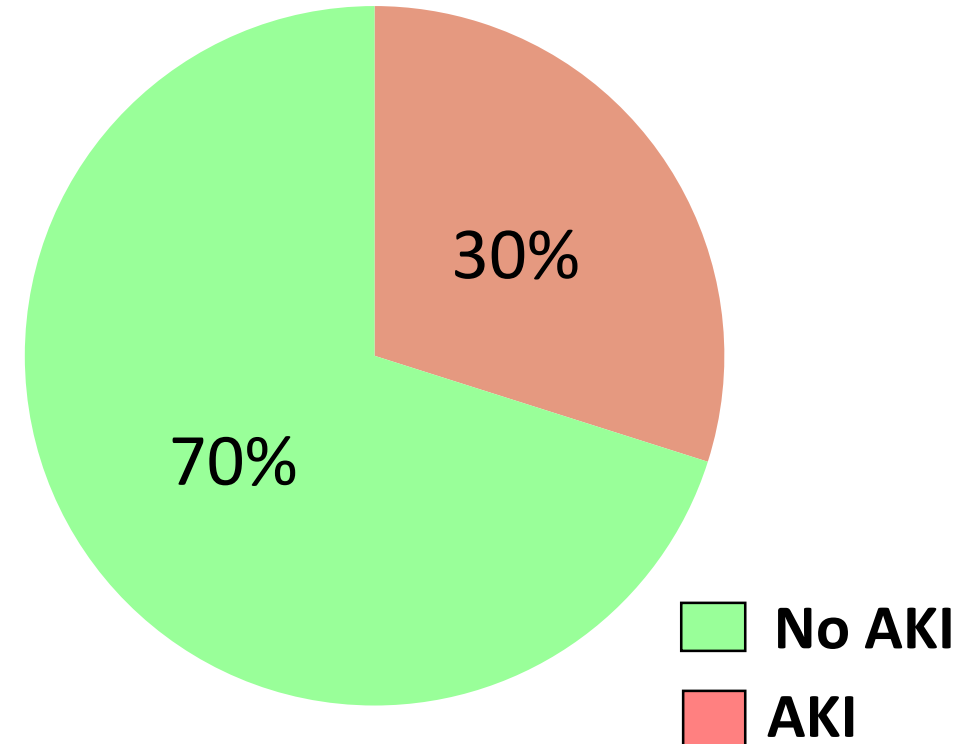
# AKI Incidence by GA



# AKI Outcomes in AWAKEN study

## Enrolled Neonates

- **Mortality Rates:**
  - **AKI: 59/605 (9.7%)**
  - **NO AKI: 20/1417 (1.4%)**
  - **$p < 0.0001$**



# Outcomes by AKI status

	Crude	p-value	Adjusted	p-value
<b>Mortality</b>	OR=7.5 (4.5 – 12.7 )	<0.0001	OR=4.6 (2.5 – 8.3)*	<0.0001
<b>Length of Stay (Days)</b>	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 Gestational Age, Mode of Delivery, Neonatal Intubation, Neonatal Chest Compression, Neonatal Saline Use, Admission for Respiratory Failure, Admission for Seizures, Admission for Hypoglycemia, Admission for Congenital Heart Disease, Neonatal Height, Neonatal Temperature, 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



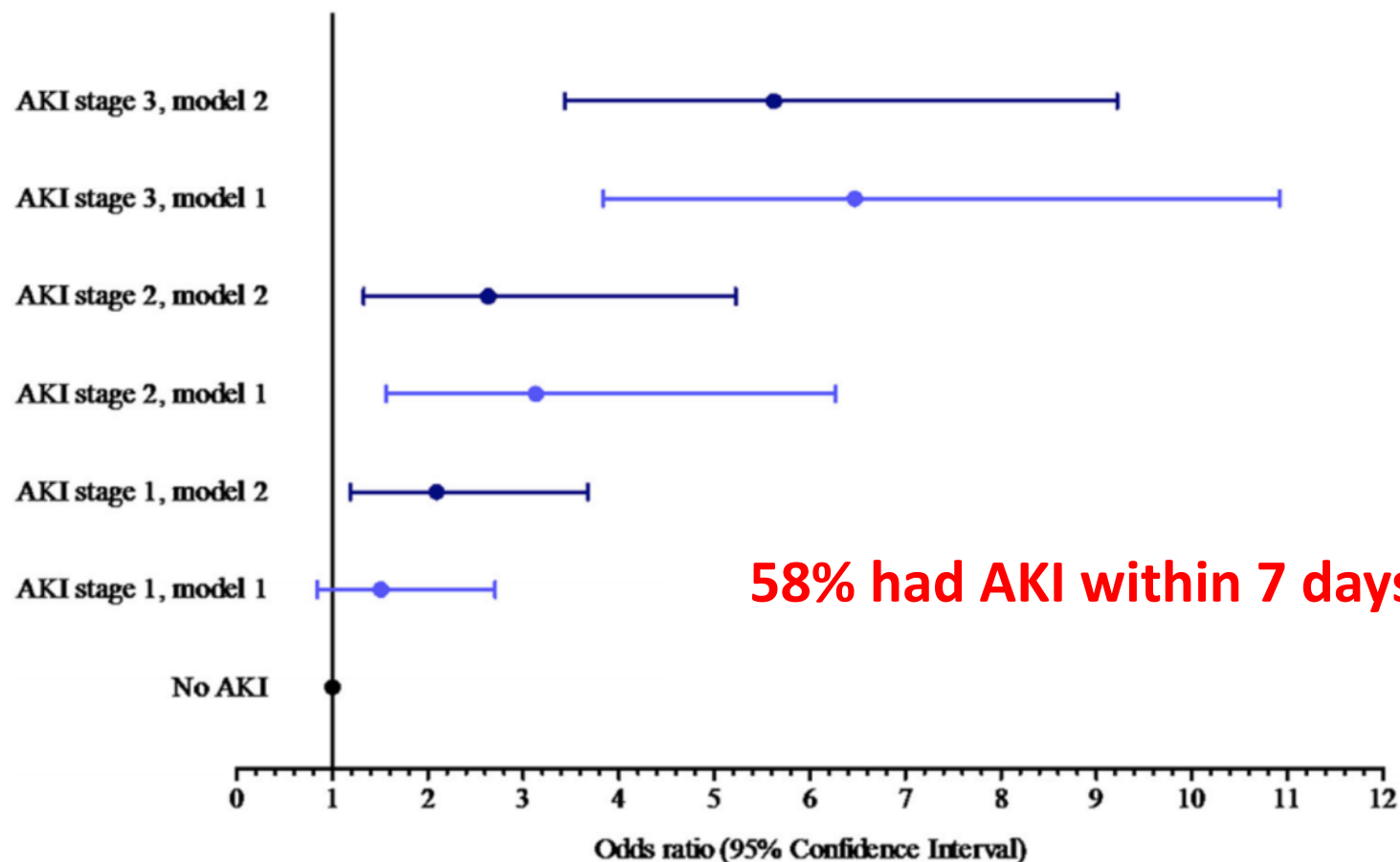


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## Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study





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# The NEW ENGLAND JOURNAL of MEDICINE

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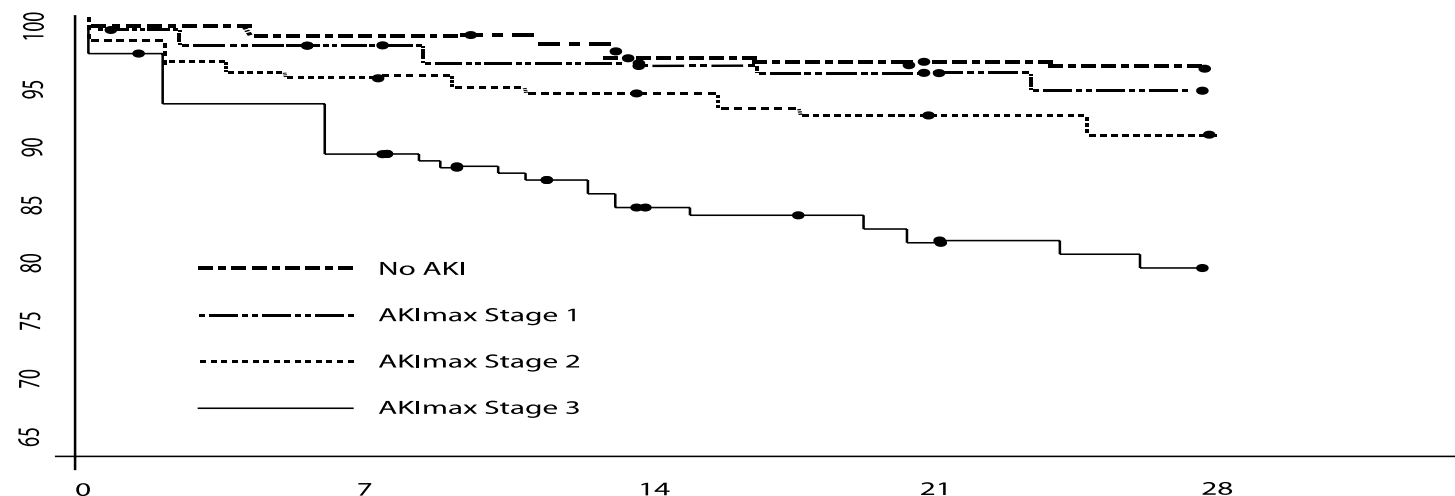
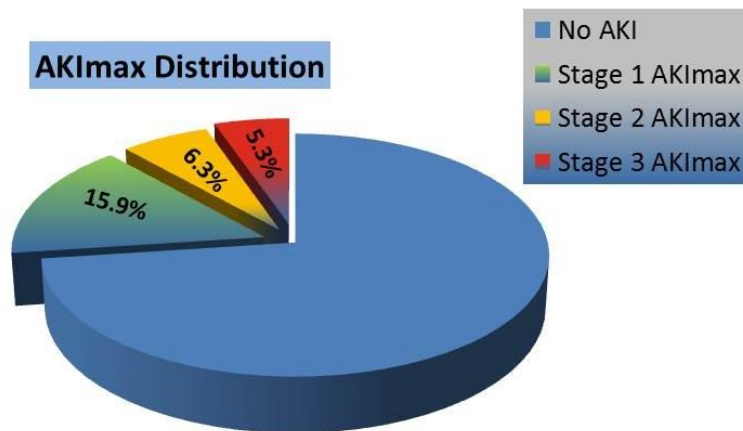
VOL. 376 NO. 1

## Epidemiology of Acute Kidney Injury in Critically Ill Children and Young Adults

Ahmad Kaddourah, M.D., Rajit K. Basu, M.D., Sean M. Bagshaw, M.D., and Stuart L. Goldstein, M.D.,  
for the AWARE Investigators\*

# AWARE

AKI within 7 days: 26.9%



Population*	ICU Day				p value		
	7	14	21	28	vs. No AKI	vs. AKI <sub>max</sub> Stage 1	vs. AKI <sub>max</sub> Stage 2
No AKI (3422)	3369	3356	3348	3339			
AKI <sub>max</sub> Stage 1 (718)	705	701	698	696	0.32		
AKI <sub>max</sub> Stage 2 (294)	286	284	282	280	0.015	0.18	
AKI <sub>max</sub> Stage 3 (249)	223	212	205	203	<0.001	NEJM 2017 <sup>1</sup>	<0.001

# Lesson # 2

- AKI impacts outcomes whether you are
  - A mouse
  - A baboon
  - A human
    - An adult in the ICU – AKI- EPI





# Lesson # 2

- AKI impacts outcomes whether you are
  - A mouse
  - A baboon
  - A human
    - An adult in the ICU – AKI EPI
    - A child in the PICU - AWARE



# Lesson # 2

- AKI impacts outcomes whether you are
  - A mouse
  - A baboon
  - A human
    - An adult in the ICU
    - A child in the PICU
    - A neonate in the NICU - AWAKEN



# Lesson # 2

- AKI impacts outcomes whether you are
  - A mouse
  - A baboon
  - A human
    - An adult in the ICU – AKI EPI
    - A child in the PICU - AWARE
    - A neonate in the NICU - AWAKEN



# Cappuccino Anyone?



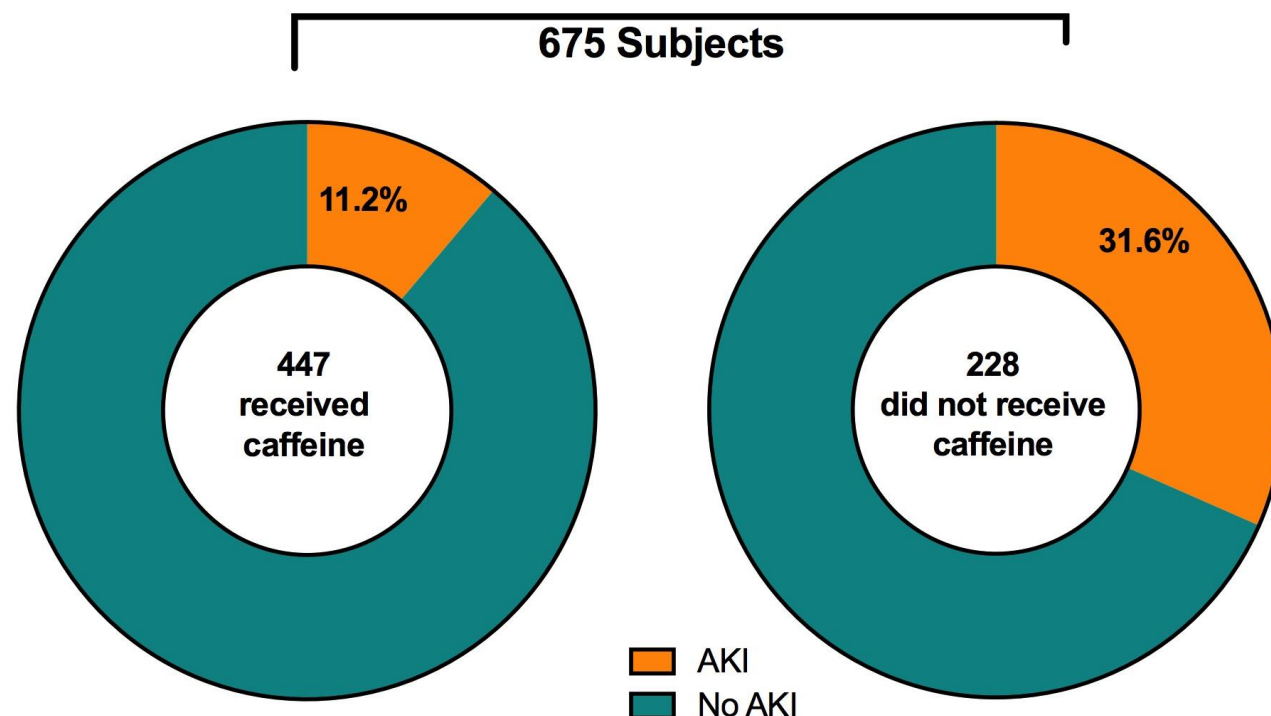
# Association Between Early Caffeine Citrate Administration and Risk of Acute Kidney Injury in Preterm Neonates

## Results From the AWAKEN Study



Matthew W. Harer, MD; David J. Askenazi, MD, MSPH; Louis J. Boohaker, MPH; J. Bryan Carmody, MD, MPH; Russell L. Griffin, PhD; Ronnie Guillet, MD, PhD; David T. Selewski, MD; Jonathan R. Swanson, MD, MSc; Jennifer R. Charlton, MD, MSc; for the Neonatal Kidney Collaborative (NKC)

- 675 premature infants
  - 22 and < 28 weeks = 204
  - >28 and < 33 weeks = 471
- **NOT BIAS BY INDICATION**  
**Babies who received Caffeine were Sicker!**





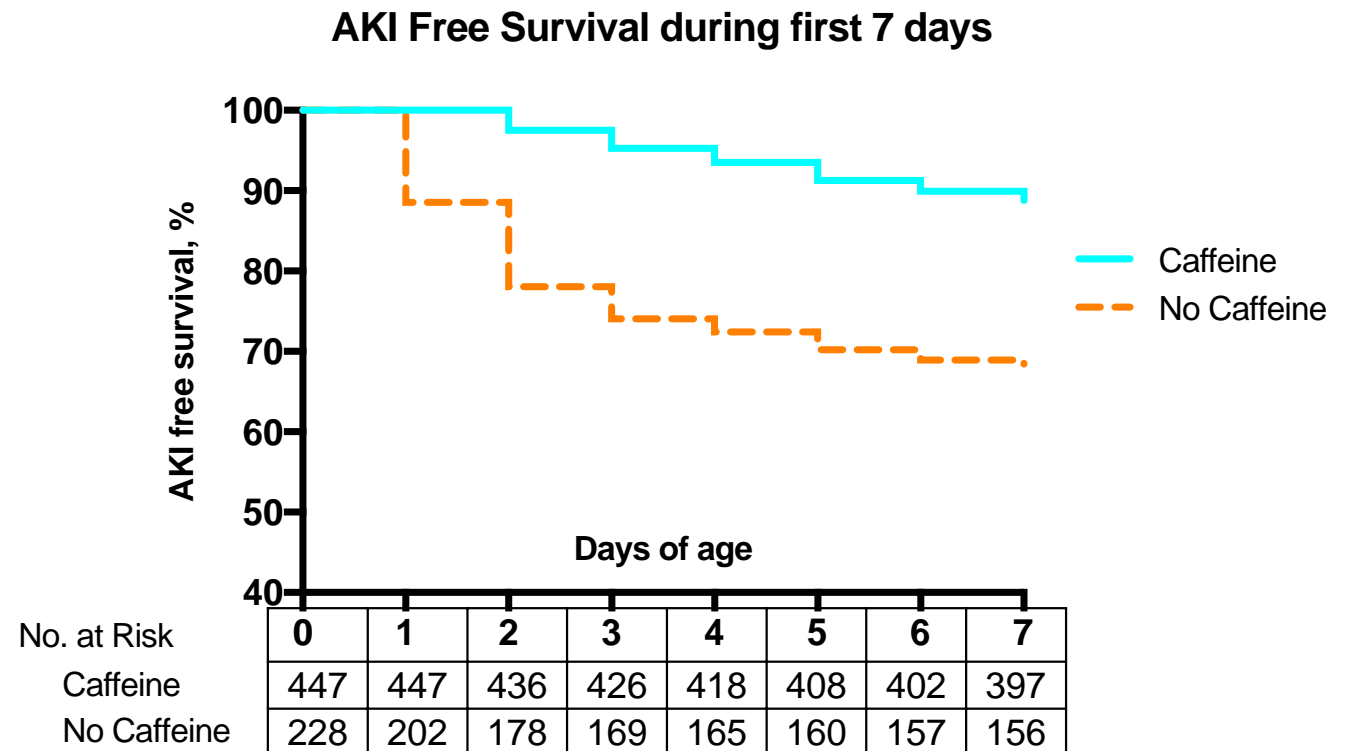
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**Babies who received Caffeine were Sicker!**





**Table 3 – Primary Acute Kidney Injury Outcomes**

	Caffeine	No Caffeine	Unadjusted OR (95% CI)	Adjusted <sup>b</sup> OR (95% CI)	NNE
<b>EARLY AKI <sup>c</sup> (&lt;7 DAYS)</b>					
Overall	50/447 (11.2%)	72/228 (31.6%)	0.28 (0.18 – 0.44)	0.20 (0.11-0.34)	4.3
Extremely preterm (<27 wks)	30/149 (20.1%)	38/55 (69.1%)	0.07 (0.03-0.16)	0.13 (0.06-0.31)	2.2
Very preterm (28-32 wks)	30/298 (6.7%)	34/173 (19.7%)	0.31 (0.16-0.61)	0.27 (0.13-0.56)	8.1
<b>ANY AKI <sup>d</sup> (&lt;120 DAYS)</b>					
Overall	103/447 (23.0%)	83/228 (36.4%)	0.56 (0.38-0.84)	0.27 (0.16-0.47)	4.4
Extremely preterm (<27 wks)	44/149 (46.3%)	44/55 (80.0%)	0.12 (0.05-0.30)	0.24 (0.10-0.58)	3.1
Very preterm (28-32 wks)	34/293 (11.6%)	39/170 (22.9%)	0.52 (0.29-0.94)	0.32 (0.16-0.62)	8.0

<sup>a</sup> Based on generalized linear mixed model with logit link and binary distribution

<sup>b</sup> Adjusted for gestational age, antibiotic use, study site type, and neonatal evaluation of sepsis

Abbreviations: OR=Odds ratio, CI=Confidence Interval, NNE=number needed to be exposed

<sup>c</sup> *p-value for interaction*<sub>preterm</sub>=0.23

<sup>d</sup> *p-value for interaction*<sub>preterm</sub>=0.62

# Lesson # 3 – Cappuccino with Claudio to prevent AKI ?



# Why do babies get AKI?

*aha moment*

a moment of sudden  
realization, inspiration,  
insight, recognition,  
or comprehension

*Definition from the Merriam-Webster Dictionary*

Timing  
is  
everything

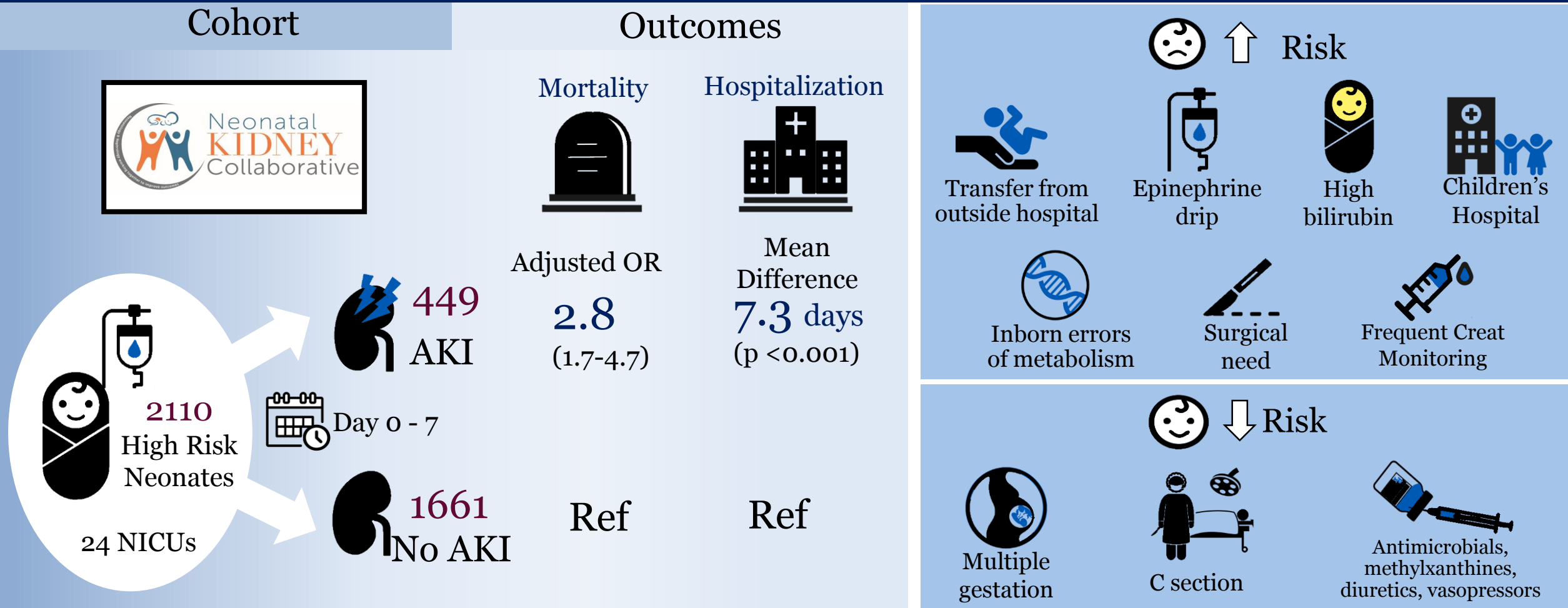


# What is Early Vs. Late AKI

- EARLY after birth
  - Prenatal Kidney health
  - Cardiopulmonary Transition after birth
  - Delivery process/resuscitation
  - Early Sepsis/shock
  - Acute fluid changes
  - Maternal Medications
- LATER
  - Traditional AKI risk factors
    - Sepsis
    - Meds
    - Shock



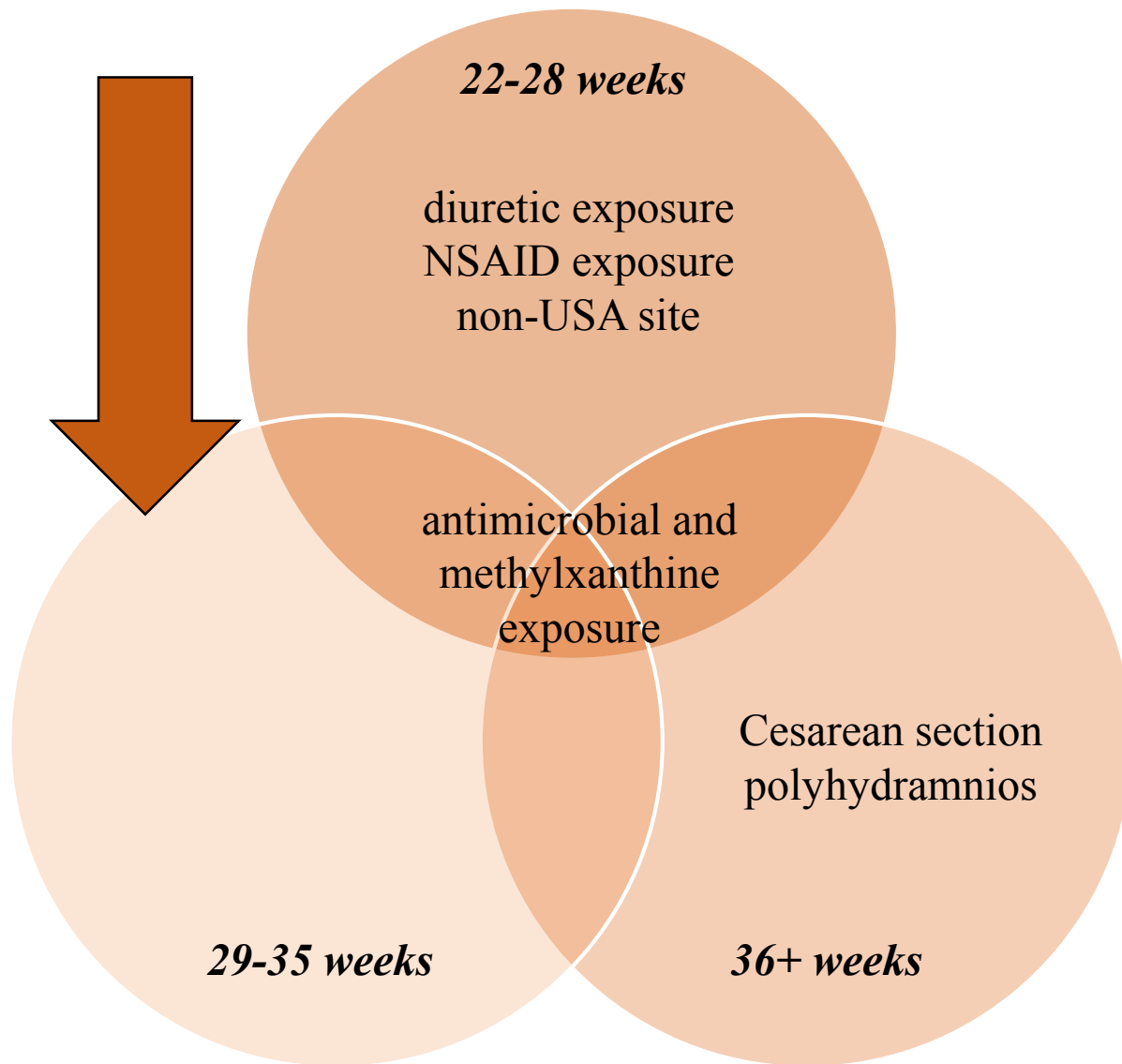
# Risk Factors and Outcomes of **Early** Onset Neonatal AKI AWAKEN Study



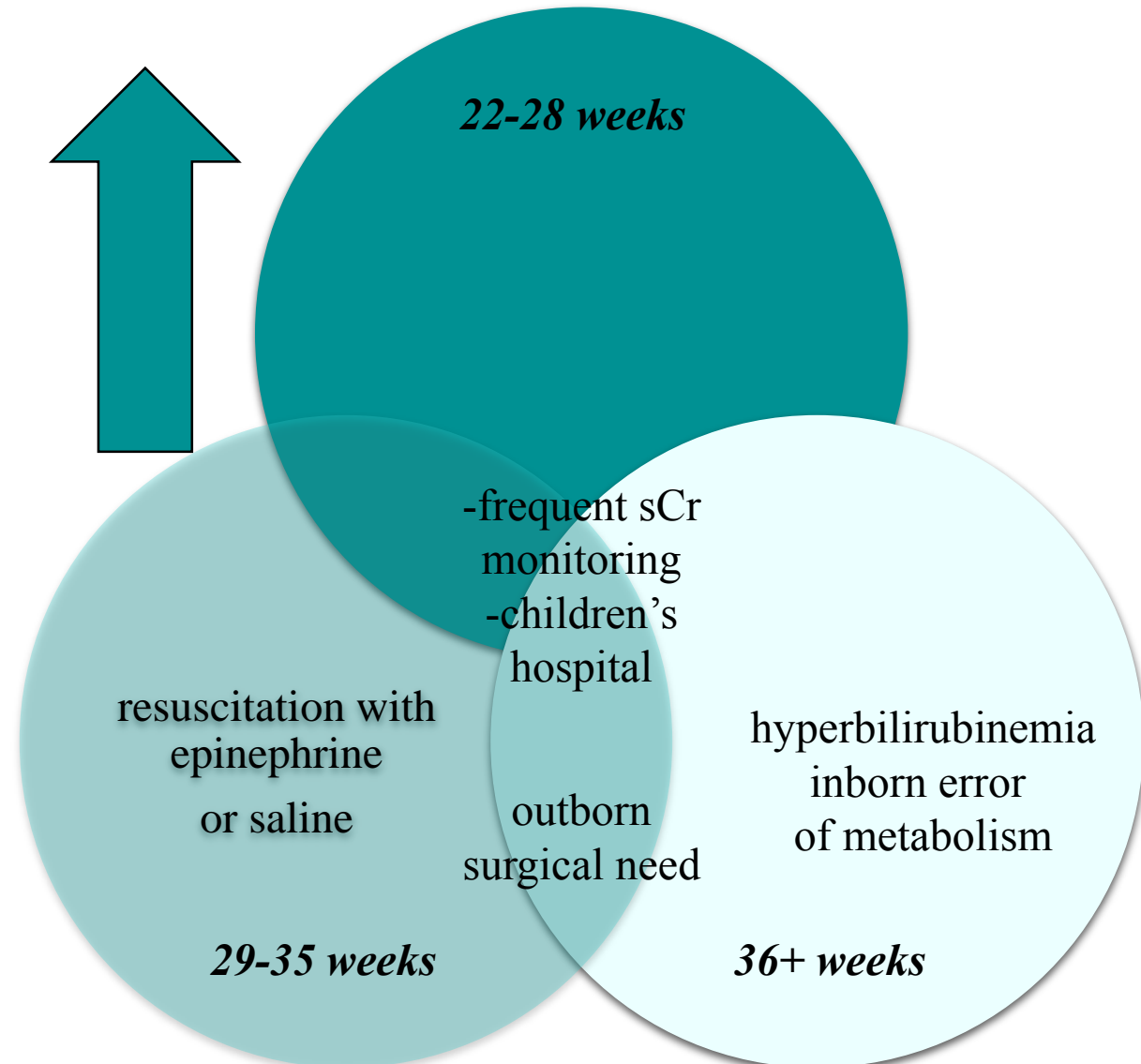
**Conclusions** AKI in the first postnatal week is common & associated with death and longer hospitalizations. The AWAKEN study demonstrates specific risk factors which can serve as “red flags”.

Jennifer Charlton, Louis Boohaker, David Askenazi, Alison Kent, et al., on behalf of the NKC. *Incidence and Risk Factors of Early Onset Neonatal Acute Kidney Injury*. CJASN doi: 10.2215/CJN.03670318.  
**Visual Abstract by Divya Bajpai, MD, PhD.**





**Factors associated with lower risk for early AKI in each gestational age group**



**Factors associated with higher risk for early AKI in each gestational age group**






Clinical Research Article | Published: 13 December 2018

# Late onset neonatal acute kidney injury: results from the AWAKEN Study

Jennifer R. Charlton , Louis Boohaker, David Askenazi, Patrick D. Brophy, Mamta Fuloria, Jason Gien, Russell Griffin, Sangeeta Hingorani, Susan Ingraham, Ayesa Mian, Robin K. Ohls, Shantanu Rastogi, Christopher J. Rhee, Mary Revenis, Subrata Sarkar, Michelle Starr, Alison L. Kent & on behalf of the Neonatal Kidney Collaborative (NKC)

*Pediatric Research* **85**, 339–348 (2019) | [Download Citation](#) 

Factors that increase or decrease risk for **LATE** AKI,  $c=0.88$

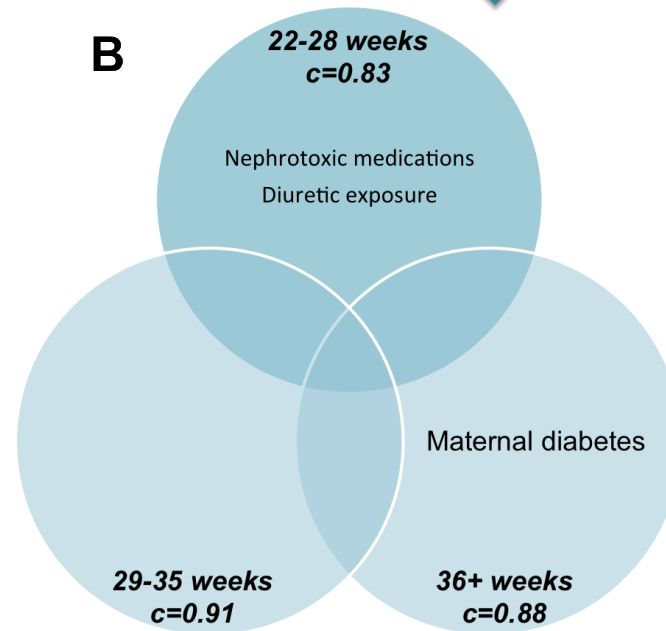
Data not published

**A**

- Increased gestational age
- Multiple gestations
- Diuretic exposure

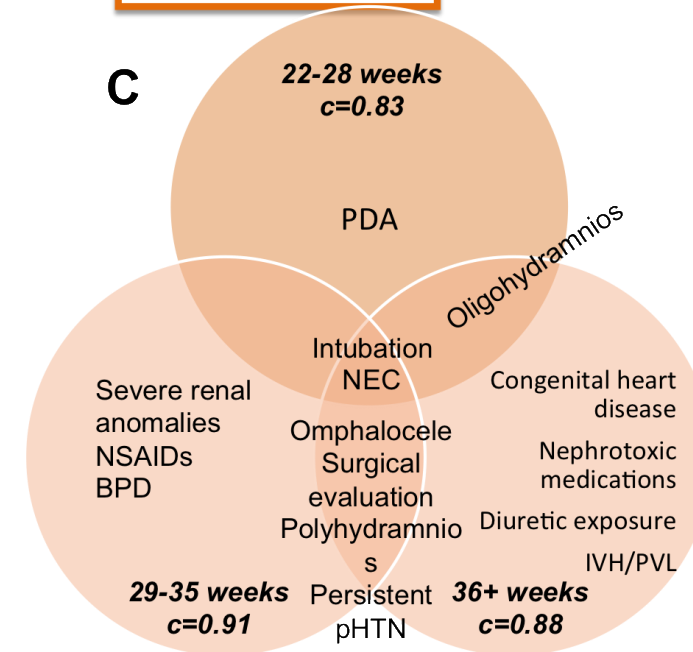
- Intubation
- Congenital heart disease
- Omphalocele
- Surgical evaluation
- Mild-severe renal anomalies
- Oligohydramnios
- Polyhydramnios
- Vasopressor exposure
- NSAID exposure
- BPD
- Persistent pulmonary HTN
- NEC

**B**



Factors that decrease risk for LATE AKI in each gestational age group

**C**



Factors that increase risk for LATE AKI in each gestational age group

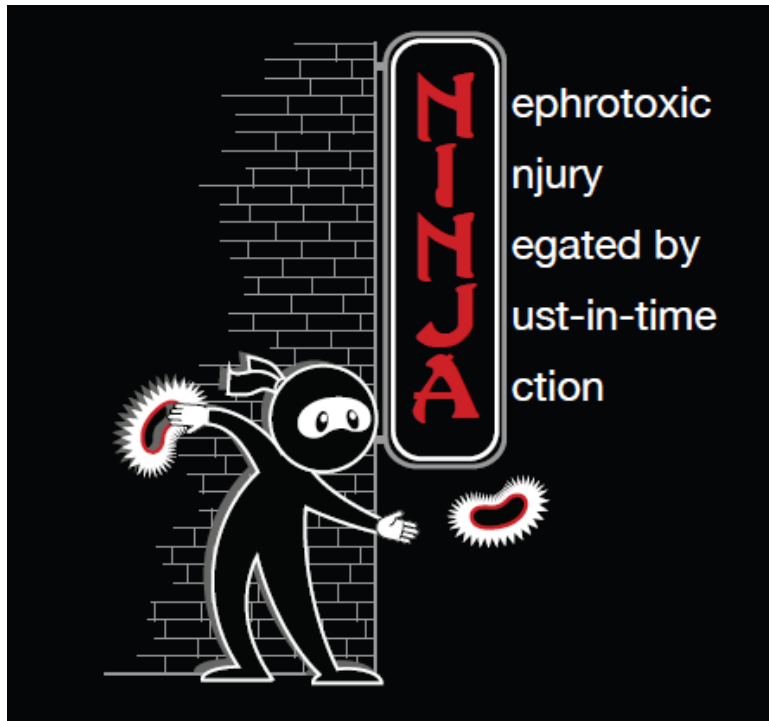
# Lesson #4

- The incidence and risk factors for AKI in your unit may not be the same for a given period of time.
  - Immediately after surgery vs. later in the hospital course
  - During the immediate septic shock course vs. later in the ICU stay
- Consider that different populations within your ICU may have different risk factors for AKI
  - Difference by age?
  - Difference by underlying condition?
  - Differences in nephron numbers (CKD) when they arrive to the ICU



# So what....what can RISK assessment do for you?

- Helps you be proactive rather than reactive



# Methods

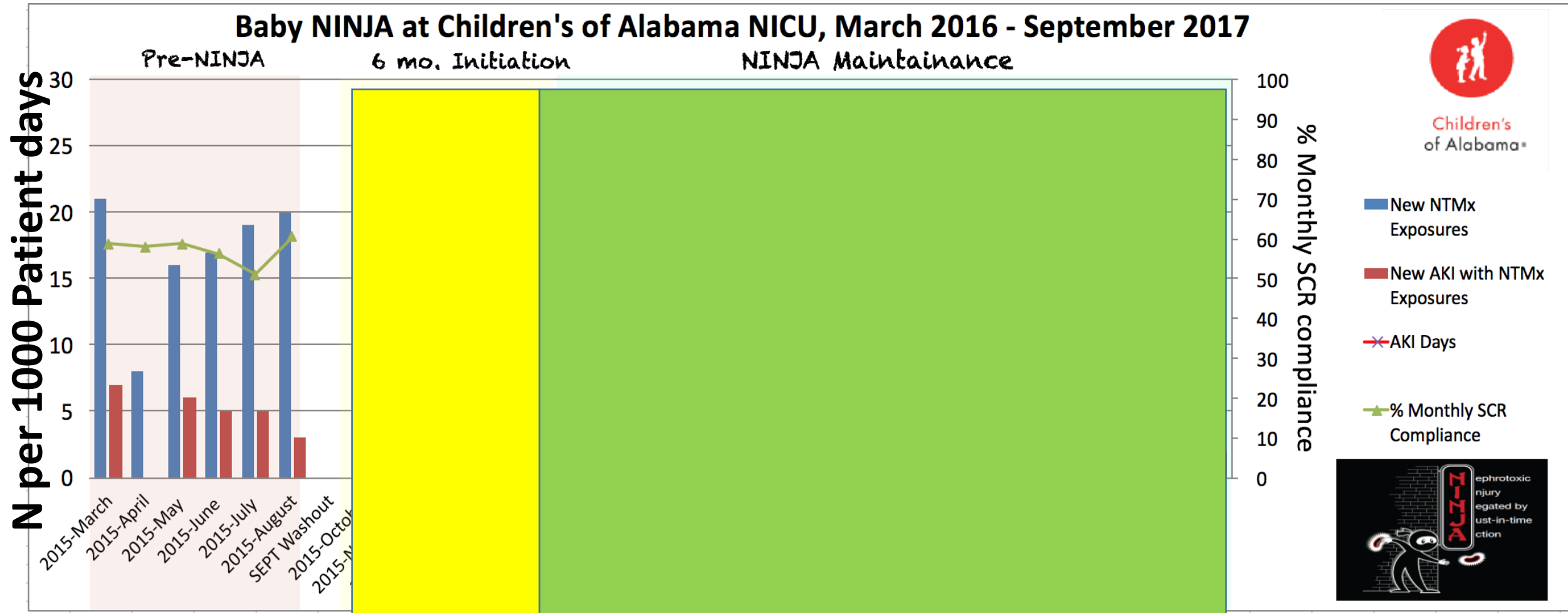
- **Daily screening for**
  - 3 or more days of Vanc or Aminoglycosides
  - 3 or more NTM meds at the same time
- **Clinicians PAY ATTENTION**

## Results

- **Divided into 3 Eras:**
  - **Pre-NINJA Era:** 6-mo retrospective chart review  
*1-mo washout period*
  - **NINJA Initiation Era:** 6-mo baseline assessment after NINJA implementation
  - **NINJA Sustainability Era:** 18-mo NINJA maintenance



# BABY NINJA





# Lesson # 5

- Let your risk factors work for you – Be proactive
- Nephrotoxic AKI is a preventable disease
- You Too Can Be a NINJA



# Renal Support/ Dialysis in Neonates

- Only 4% patients with AKI in AWAKEN received Dialysis
- Historically - Technically very difficult
- Even with the best practices....
  - CRRT exposes the smallest children to added risk



≠



# My neonatologist used to HATE CRRT

- The machines don't run very well
  - Alarms going up all night
  - Circuits clot all the time
- Nurses very confused about the therapy
- They always 'crash' when we start CRRT
- Catheters are a pain to put in and manage
- Used as a "last resort" --- sometimes
- Too 'RISKY'



# We addressed these concerns!

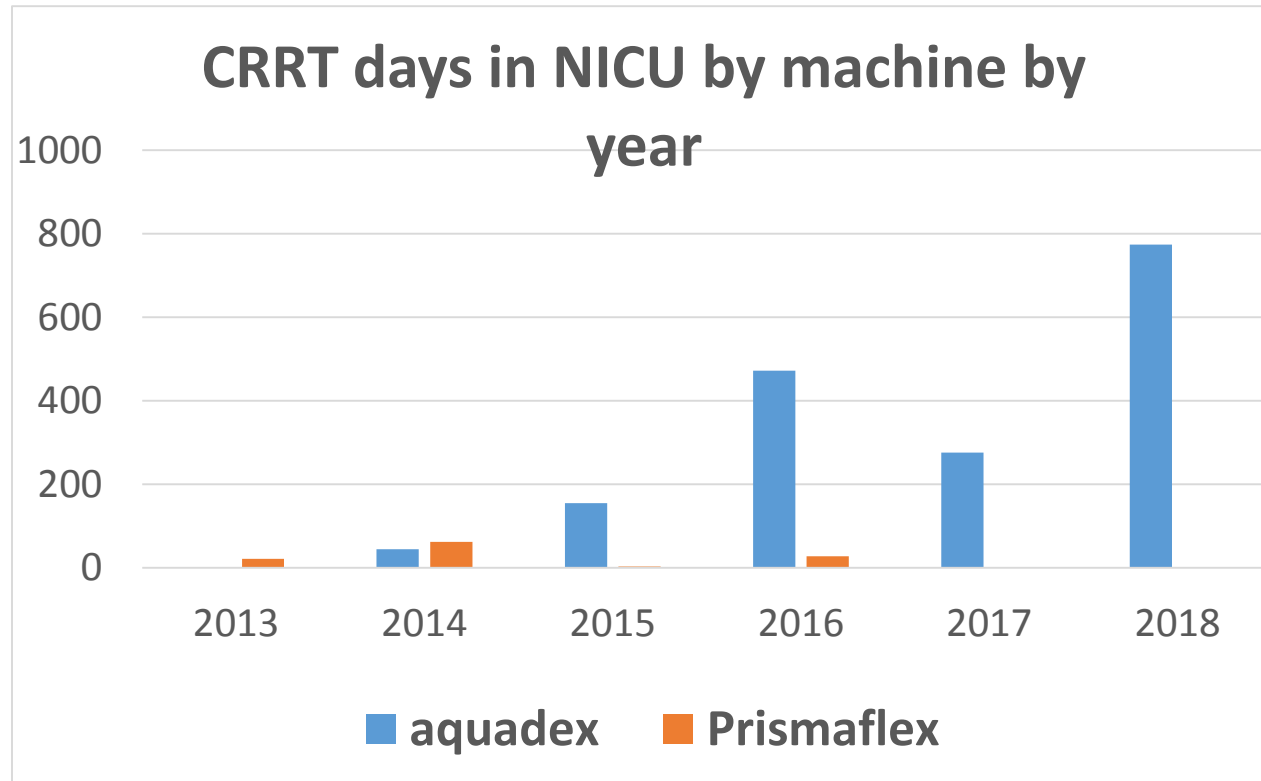
**Figure 2: Pre-Filter CVVH**



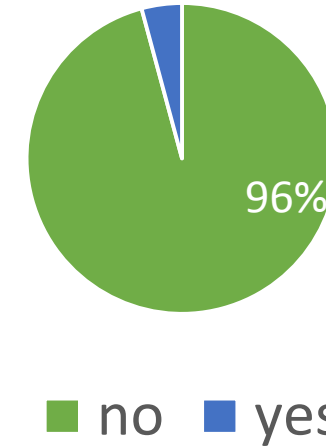
- Enhanced training
  - Quarterly classes for NICU
  - 57 NICU nurses trained last year
- Enhance QI
  - Yearly review of NICU specific patients
- Worked with Surgery to figure out optimal catheters”



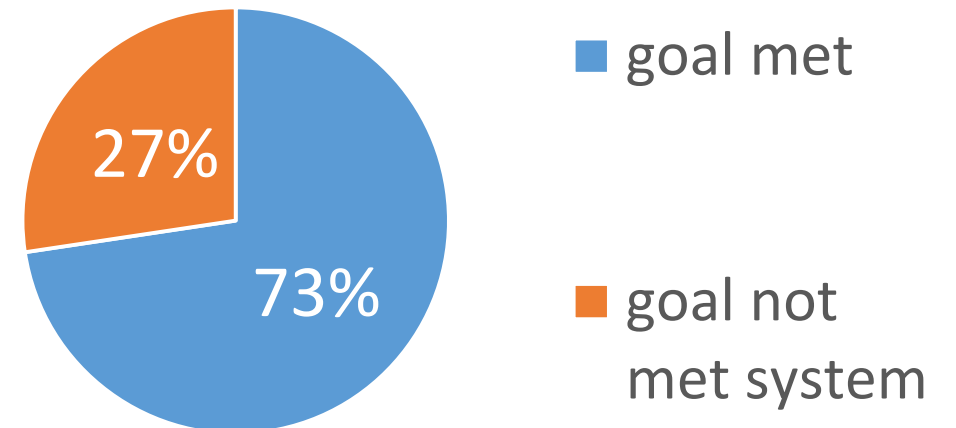
# NICU – Specific QI data



## Hypotension Requiring Intervention at Intervention



## Non-Patient Issue Circuit Survival (>60 hrs)



# Lesson # 6

- identify and address the challenges to provide great CRRT care...  
You can change the minds of even your biggest skeptics.
- Its easy to complain and say ...
  - “The ICU doesn’t get it ....they call us way too late”
  - “The nephrologist are never around they just walk by and look at the machine and don’t really help out”
- Take time to invest in your CRRT Program
  - Education
  - QI
  - Communication
  - ‘thinking outside the box” approach





# Lessons learned from Neonatal AKI

1. Collaboration is vital!
2. AKI is bad – No matter your size
3. The time course of the disease and the type of patient affect AKI development
4. Caffeine may protect against AKI
5. Nephrotoxic AKI is a preventable disease
6. By addressing the challenges to providing great CRRT care, you can change the minds of even your biggest skeptics.





# Thanks

David Askenazi MD, MSPH

Director of Pediatric and Infant Center for Acute Nephrology (PICAN)

Professor of Pediatrics – UAB

[daskenazi@peds.uab.edu](mailto:daskenazi@peds.uab.edu)