AKI in Neonates
Epidemiology and Outcomes

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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)

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
-- $$
Preterm neonates

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

Nephrogenesis begins at 9 weeks

Completed ~36 weeks

60% occurs during the third trimester

Nephrons can’t regenerate
• Neonatal AKI workshop
  • Sponsored by the NIH NIDDK - April 2013
    • Marva Moxey Mimms MD - Program Officer at NIH
    • Multiple gaps in knowledge
    • Brough 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
The NKC includes at least one neonatologist and one nephrologist from 24 institutions in 4 countries: USA, Canada, Australia, and India.
Thanks to all who are helping to AWAKEN the field of Neonatal AKI

<table>
<thead>
<tr>
<th>Children's Hospital at Montefiore</th>
<th>Stony Brook University</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Rochester</td>
<td>Children's National Med Center</td>
</tr>
<tr>
<td>University of Iowa</td>
<td>McGill University</td>
</tr>
<tr>
<td>University of Michigan</td>
<td>University of British Columbia</td>
</tr>
<tr>
<td>University of New Mexico</td>
<td>University of Virginia</td>
</tr>
<tr>
<td>University of Washington</td>
<td>Texas Children's Hospital</td>
</tr>
<tr>
<td>University of Alabama at BHM</td>
<td>Maimonides Medical Center</td>
</tr>
<tr>
<td>Cincinnati Children's Hospital</td>
<td>Canberra Hospital</td>
</tr>
<tr>
<td>University of Kentucky</td>
<td>The Medicity Hospital</td>
</tr>
<tr>
<td>University of Miami</td>
<td>Children's Hospital Colorado</td>
</tr>
<tr>
<td>Metrohealth Medical Center</td>
<td>St. Louis Children's</td>
</tr>
<tr>
<td>Nationwide Children’s</td>
<td>Tuft’s - Boston</td>
</tr>
</tbody>
</table>
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

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

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

Published on September 7th, 2017 – Lancet: Child and Adolescents - online first
AWAKEN: Breakdown of Screened vs. Enrolled NICU admissions from Jan 1 – March 31, 2014

Total Number of Patients Screened (n = 4273)

- Enrolled (n = 2162)
  - Less than 2 SCr and no UOP (n = 140)
  - Final Sample (n = 2022)

- Not Enrolled* (n = 2111)
  - Not admitted to NICU during study period (n = 60)
  - No IVFs for at least 48 hours (n = 1793)
  - Age > 14 days at NICU admission

*Some patients were not enrolled due to various reasons.
## Neonatal AKI definition

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum Creatinine (SCr)</th>
<th>Urine Output (UOP)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No change in SCr or rise &lt; 0.3 mg/dL</td>
<td>&gt; 1 ml/kg/hour</td>
</tr>
<tr>
<td>1</td>
<td>SCr rise ≥ 0.3 mg/dl within 48 hrs or SCr rise ≥ 1.5 - 1.9 X reference SCr*</td>
<td>&gt; 0.5 and ≤ 1 ml/kg/hour</td>
</tr>
<tr>
<td>2</td>
<td>SCr rise ≥ 2 to 2.9 X reference SCr*</td>
<td>&gt; 0.3 and ≤ 0.5 ml/kg/hour</td>
</tr>
<tr>
<td>3</td>
<td>SCr rise ≥ 3 X reference SCr * or SCr ≥ 2.5 mg/dl or Receipt of dialysis</td>
<td>≤ 0.3 ml/kg/hour</td>
</tr>
</tbody>
</table>

*reference value is lowest previous value

**includes days #2-7 only (day of birth = day #1)
AKI Incidence in AWAKEN study

All Enrolled Neonates

- 70% No AKI
- 30% AKI
AKI Incidence by GA

- **45%** GA 29-36 (N=916)
- **41%** GA 36+ (N=833)
- **14%** GA 22-29 (N=273)
AKI incidence by GA

- **GA 22-29**
  - No AKI: 57%
  - AKI: 43%

- **GA 29-36** (N=916)
  - No AKI: 45%
  - AKI: 55%

- **GA 36+** (N=833)
  - No AKI: 41%
  - AKI: 59%

Legend:
- Green: No AKI
- Red: AKI
AKI Incidence by GA

GA 22-29 (N=273)
- No AKI: 57%
- AKI: 43%

GA 29-36 (N=916)
- No AKI: 82%
- AKI: 18%

GA 36+ (N=833)
- No AKI: 41%
- AKI: 45%
AKI Outcomes in AWAKEN study

- Mortality Rates:
  - AKI: 59/605 (9.7%)
  - NO AKI: 20/1417 (1.4%)
  - p<0.0001
### Outcomes by AKI status

<table>
<thead>
<tr>
<th></th>
<th>Crude</th>
<th>p-value</th>
<th>Adjusted</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td>OR=7.5 (4.5 – 12.7)</td>
<td>&lt;0.0001</td>
<td>OR=4.6 (2.5 – 8.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Length of Stay</strong></td>
<td>Parameter Estimate 14.9 (11.6 – 18.1)</td>
<td>&lt; 0.0001</td>
<td>Parameter Estimate*** 8.8 (6.1 – 11.5)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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

58% had AKI within 7 days
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

AKI within 7 days: 26.9%

<table>
<thead>
<tr>
<th>AKImax Distribution</th>
<th>No AKI</th>
<th>Stage 1 AKImax</th>
<th>Stage 2 AKImax</th>
<th>Stage 3 AKImax</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKImax Stage 1 (718)</td>
<td>3369</td>
<td>3356</td>
<td>3348</td>
<td>3339</td>
</tr>
<tr>
<td>AKImax Stage 2 (294)</td>
<td>705</td>
<td>701</td>
<td>698</td>
<td>696</td>
</tr>
<tr>
<td>AKImax Stage 3 (249)</td>
<td>286</td>
<td>284</td>
<td>282</td>
<td>280</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Population*</th>
<th>ICU Day</th>
<th>vs. No AKI</th>
<th>vs. AKImax Stage 1</th>
<th>vs. AKImax Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No AKI (3422)</td>
<td>7</td>
<td>14</td>
<td>21</td>
<td>28</td>
</tr>
<tr>
<td>AKImax Stage 1</td>
<td>705</td>
<td>701</td>
<td>698</td>
<td>696</td>
</tr>
<tr>
<td>AKImax Stage 2</td>
<td>286</td>
<td>284</td>
<td>282</td>
<td>280</td>
</tr>
<tr>
<td>AKImax Stage 3</td>
<td>223</td>
<td>212</td>
<td>205</td>
<td>203</td>
</tr>
</tbody>
</table>
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 - AWAKE
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

675 premature infants
- 22 and < 28 weeks = 204
- >28 and < 33 weeks = 471

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

NOT BIASED BY INDICATION
Babies who received Caffeine were Sicker!

AKI Free Survival during first 7 days

<table>
<thead>
<tr>
<th>Days of Age</th>
<th>Caffeine</th>
<th>No Caffeine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>447</td>
<td>228</td>
</tr>
<tr>
<td>1</td>
<td>447</td>
<td>202</td>
</tr>
<tr>
<td>2</td>
<td>436</td>
<td>178</td>
</tr>
<tr>
<td>3</td>
<td>426</td>
<td>169</td>
</tr>
<tr>
<td>4</td>
<td>418</td>
<td>165</td>
</tr>
<tr>
<td>5</td>
<td>408</td>
<td>160</td>
</tr>
<tr>
<td>6</td>
<td>402</td>
<td>157</td>
</tr>
<tr>
<td>7</td>
<td>397</td>
<td>156</td>
</tr>
</tbody>
</table>
### Table 3 – Primary Acute Kidney Injury Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Caffeine</th>
<th>No Caffeine</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>NNE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EARLY AKI</strong> (&lt;7 DAYS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>50/447</td>
<td>72/228</td>
<td>0.28 (0.18 – 0.44)</td>
<td>0.20 (0.11-0.34)</td>
<td>4.3</td>
</tr>
<tr>
<td>Extremely preterm (&lt;27 wks)</td>
<td>30/149</td>
<td>38/55</td>
<td>0.07 (0.03-0.16)</td>
<td>0.13 (0.06-0.31)</td>
<td>2.2</td>
</tr>
<tr>
<td>Very preterm (28-32 wks)</td>
<td>30/298</td>
<td>34/173</td>
<td>0.31 (0.16-0.61)</td>
<td>0.27 (0.13-0.56)</td>
<td>8.1</td>
</tr>
<tr>
<td><strong>ANY AKI</strong> (&lt;120 DAYS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>103/447</td>
<td>83/228</td>
<td>0.56 (0.38-0.84)</td>
<td>0.27 (0.16-0.47)</td>
<td>4.4</td>
</tr>
<tr>
<td>Extremely preterm (&lt;27 wks)</td>
<td>44/149</td>
<td>44/55</td>
<td>0.12 (0.05-0.30)</td>
<td>0.24 (0.10-0.58)</td>
<td>3.1</td>
</tr>
<tr>
<td>Very preterm (28-32 wks)</td>
<td>34/293</td>
<td>39/170</td>
<td>0.52 (0.29-0.94)</td>
<td>0.32 (0.16-0.62)</td>
<td>8.0</td>
</tr>
</tbody>
</table>

- Based on generalized linear mixed model with logit link and binary distribution
- 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
- \( p\)-value for interaction \( p\)-value for interaction = 0.23
- \( p\)-value for interaction \( p\)-value for interaction = 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

*Timing is everything*

Definition from the Merriam-Webster Dictionary
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”.


Visual Abstract by Divya Bajpai, MD, PhD.
Factors associated with higher risk for early AKI in each gestational age group:
- Cesarean section
- polyhydramnios
- diuretic exposure
- NSAID exposure
- non-USA site
- hyperbilirubinemia
- inborn error of metabolism
- outborn surgical need
- frequent sCr monitoring
- children’s hospital
- resuscitation with epinephrine or saline

Factors associated with lower risk for early AKI in each gestational age group:
- antimicrobial and methylxanthine exposure
- 22-28 weeks
- 29-35 weeks
- 36+ weeks
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)
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 Aminoglycocides
  • 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

Baby NINJA at Children's of Alabama NICU, March 2016 - September 2017

Pre-NINJA  6 mo. Initiation  NINJA Maintainance

N per 1000 Patient days

% Monthly SCR compliance
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!

- 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

CRRT days in NICU by machine by year

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

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