Neonatal Nephrology: New Developments

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Disclosures:

- Royalties- UpToDate
- RO1 RePairEd trial is focused on Neonatal AKI- NIDDK
Outline

- Kidney Development
- Why is Neonatal Acute Kidney Injury important?
- Definition(s)
- Epidemiology
- Approaching AKI- initial management
- Fluid is a drug & has nutritional implications
- Renal supportive therapies
- New concepts
- Future directions & considerations
Lower GFR - born into renal failure
Newborns

- **128 Millions** babies are born across the world every day
  - 4.0 million babies are born in United States each year.
  - 5.1 million babies are born in Europe each year.
- Most are either born at home, or in hospitals where they stay for a few days, then are sent home.
Newborns

- Some, however, are born without the ability to sustain life without support

In the US 2012

- 77.9 NICU admissions per 1000 live birth
  - 43.0 per 1000 for normal-birth-weight (2500-3999 g)
  - 844.1 per 1000 for very low-birth-weight (<1500 g)

4 million live births * (77.9 admission / 1000 births) = 312,000 babies a year are admitted to level 3 NICU
= 5% of all Intensive Care admissions in the US.
Some, however, are born without the ability to sustain life without support

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
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 (or near-term) Infants
  - High Morbidity
  - High Mortality
  - Mod / low LOS
  - $$
Risk Factors:
- Systemic illness
- Sepsis/hypotension
- Necrotizing enterocolitis
- Intraventricular hemorrhage
- Umbilical artery catheterization
- Perinatal depression/low Apgar scores
- Prolonged antibiotic exposure
Causes of AKI

ACUTE KIDNEY INJURY

Pre-Renal AKI
- Low blood volume
  - Hemorrhage
  - Gastric, chest tube, transepidermal losses
- Low Intravascular volume
  - Capillary leak
  - Hypoalbuminemia
- Poor cardiac output
  - Heart failure
  - Cardiac surgery/CPB
- Pharmacologic agents
  - Indomethacin
  - ACE inhibitors

Intrinsic AKI
- Any of the pre-renal causes if prolonged
- Infections
  - Sepsis, pyelonephritis
  - Congenital infections
- Vascular events
  - Renal artery/vein thrombosis
- Nephrotoxins
  - Aminoglycosides
  - Indomethacin

Post-Renal AKI
- Congenital malformations
- UPJ/ UVJ obstruction
- Neurogenic bladder
- Posterior urethral valves
- Extrinsic compression / intraluminal obstruction
- Abdominal /pelvic masses
- Renal calculi
- Fungus balls
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Definition</th>
<th>Incidence of AKI</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Askenazi et al, 2009</td>
<td>Very Low Birth weight Infants (n=195)</td>
<td>AKIN criteria</td>
<td>Matched case – control study</td>
<td>AKI is associated with increased mortality after adjustment for confounders</td>
</tr>
<tr>
<td>Koralkar et al, 2011</td>
<td>Very Low Birth weight Infants (n=229)</td>
<td>Neonatal Modified KDIGO criteria</td>
<td>18%</td>
<td>Adjusting for severity of illness AKI was associated with increased mortality</td>
</tr>
<tr>
<td>Rhone et al, 2013</td>
<td>Very Low Birth weight Infants (n=107)</td>
<td>Neonatal Modified KDIGO criteria</td>
<td>26.2%</td>
<td>AKI is associated with nephrotoxic medication exposure.</td>
</tr>
<tr>
<td>Carmody et al, 2014</td>
<td>Very Low Birth weight Infants (n=455)</td>
<td>Neonatal Modified KDIGO criteria</td>
<td>39.8%</td>
<td>AKI associated with increased mortality and length of stay adjusted for severity of illness.</td>
</tr>
<tr>
<td>Study</td>
<td>Population</td>
<td>Definition</td>
<td>Incidence of AKI</td>
<td>Findings</td>
</tr>
<tr>
<td>------------------</td>
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<td>-----------------------------</td>
<td>------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Kaur et al, 2011</strong></td>
<td>Perinatal Asphyxia (n=36)</td>
<td>AKIN criteria</td>
<td>41.7%</td>
<td>AKIN capture AKI previously missed by previous standard of SCr &gt; 1.5 mg/dl</td>
</tr>
<tr>
<td><strong>Askenazi et al, 2013</strong></td>
<td>Sick near-term neonates (n=58)</td>
<td>Neonatal Modified KDIGO criteria</td>
<td>15.6%</td>
<td>AKI associated with increased mortality and positive fluid balance</td>
</tr>
<tr>
<td><strong>Selewski et al, 2013</strong></td>
<td>Perinatal Asphyxia (n=96)</td>
<td>Neonatal Modified KDIGO criteria</td>
<td>38%</td>
<td>AKI predicted prolonged mechanical ventilation, length of stay, and abnormal brain MRI findings at 7-10 days of life</td>
</tr>
</tbody>
</table>
The NKC includes at least one neonatologist and one nephrologist from 24 institutions in 4 countries: USA, Canada, Australia and India.
Assessment
Worldwide
Acute
Kidney
Epidemiology
Neonates

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

Published on September 7th, 2017 – Lancet: Child and Adolescents - online first
AWAKEN methods

- Multi-center retrospective cohort study
  - 24 level 2-4 NICUs
- All NICU admissions from Jan 1 – March 31, 2014

Inclusion criteria
- Admission during the study period
- Provision of at least 48 hours of IV fluids

Exclusion criteria
- Admission at > 2 weeks of life
- Newborns requiring congenital heart disease repair < 7 days of life
- Death within 48 hours of admission
- Lethal chromosomal anomaly
- Severe, bilateral congenital kidney and urinary tract disease
# 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)
AWAKEN: Breakdown of Screened vs. Enrolled

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)
AKI Incidence in AWAKEN study

All Enrolled Neonates

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

- 41% (GA 22-29)
- 45% (N=273)
AKI incidence by GA

GA 22-29

- No AKI: 57%
- AKI: 43%

Total: 41% No AKI, 14% AKI (N=273)
AKI Incidence by GA

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

- **GA 29-36**
  - No AKI: 82%
  - AKI: 18%
AKI Incidence by GA

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

- **GA 29-36**
  - 18% AKI

- **GA 36+**
  - 37% No AKI
  - 63% AKI

Legend:
- Green: No AKI
- Red: AKI
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 (Days)</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
Huge Practice Variation (screening for AKI)
- High Range for the Median # SCr/ baby differed by center = 1 – 12
- High Range for the incidence of AKI across centers = 3% vs. 56%

We **have answered many questions**
- Incidence of Neonatal AKI using KDIGO = 30%
- Neonates with AKI have 4.6 time higher odds of death and almost 9 more hospital days after controlling for numerous confounders

We **are going to answer many more questions**
- 4 papers published
- 7 additional papers have been submitted for publication
- 6 additional papers in preparation

We **are going to AWAKEN the community.**
- It will no longer be acceptable for doctors caring for sick neonates to ignore this vital organ
675 premature infants
- 22 and < 28 weeks = 204
- >28 and < 33 weeks = 471

Babies who received Caffeine were Sicker!


**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></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;7 DAYS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>50/447 (11.2%)</td>
<td>72/228 (31.6%)</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 (20.1%)</td>
<td>38/55 (69.1%)</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 (6.7%)</td>
<td>34/173 (19.7%)</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></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;120 DAYS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>103/447 (23.0%)</td>
<td>83/228 (36.4%)</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 (46.3%)</td>
<td>44/55 (80.0%)</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 (11.6%)</td>
<td>39/170 (22.9%)</td>
<td>0.52 (0.29-0.94)</td>
<td>0.32 (0.16-0.62)</td>
<td>8.0</td>
</tr>
</tbody>
</table>

\(^a\) Based on generalized linear mixed model with logit link and binary distribution

\(^b\) 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

\(^c\) p-value for interaction caffeine = 0.23

\(^d\) p-value for interaction preterm = 0.62
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

New NTMx Exposures
New AKI with NTMx Exposures
AKI Days
% Monthly SCR Compliance
Current Approaches to Renal Supportive Therapy and AKI

- Conservative management
- Non-dialytic interventions
- Renal replacement therapies
- New concepts
• **Goals**
  - Evaluation
  - Prevent complications
  - Prevent the need for dialysis
  - Prevent morbidity and mortality

• **Strategies**
  - **Proven curative or preventive therapies**
  - *Treatment of AKI remains largely supportive*
How do we define success?

- Decrease mortality
- Decrease morbidity
- Shorten NICU length of stay
- Shorten time to extubation
- Minimize progression to chronic kidney disease
**Management**

- Fluid bolus (crystallloid) if oliguric
- Role of diuretics?
- Consider dopamine if heart failure of hypotensive
- Restriction of fluids to insensible loss
- Maintain electrolyte balance
  - K+, PO4, CA2+, AMINO ACIDS
- Discuss with your friendly nephrologist
  - **WATCHFUL WAITING?**
  - **RESTRICT NUTRITION (SEEMS COUNTER INTUITIVE)**
  - **WHY DO WE WAIT TO TAKE CARE OF THE KIDNEYS?**
Current Approaches to Renal Supportive Therapy and AKI

- Conservative management
- Non-dialytic interventions
- Renal replacement therapies
- New concepts
Dopamine

- **Rationale**: increase renal perfusion in the sick pre-term and term infant with pre-renal azotemia caused by hypoxemia, acidosis, or indomethacin administration

Therapeutics

What is out there

- **Dopamine**
  - **Outcomes**: Well powered RCTs in adults with AKI have shown no improvement in survival, length of hospital stay, or need for dialysis using “renal dose” dopamine
    - These studies have not been performed in children or neonates

Fenoldopam

**Rationale:** selective and potent DA-1 agonist → systemic/renal vasodilation that maintains renal blood flow and kidney tissue oxygenation and may increase UO
Fenoldopam

**Outcomes:** 2 small, prospective studies in infants with CHD undergoing CPB

- **LOW DOSE (0.1 mcg/kg)** - no improvement in outcomes (inotropic support, AKI incidence, fluid balance, time to extubation, etc.)
- **HIGH DOSE (1 mcg/kg)** – reduction in uNGAL and uCysC levels, diuretic and vasodilator administration


*Figure 2 Urinary neutrophil gelatinase-associated lipocalin (uNGAL) levels. A significant increase of uNGAL levels from baseline (T0) to ICU admission (T1) and a consequent decrease after 12 hours (T2) was observed in both groups (P = 0.025). However, uNGAL values were significantly reduced in group F at T1 (P = 0.002) and T2 (P = 0.04) compared with group C (*).*

*Ricci et al. Critical Care 2011, 15:R160 http://ccforum.com/content/15/3/R160*
Theophylline

Rationale: adenosine antagonist that may inhibit adenosine-induced renal vasoconstriction following hypoxic/ischemic event and therefore ameliorate renal dysfunction in asphyxiated neonates
Theophylline

- **Outcomes:** 3 small RCTs in term asphyxiated infants and 1 small RCT in pre-term infants

- 5-8 mg/kg one time during first 60 minutes of life
- Theophylline groups had better fluid balance, less AKI, and better GFR

<table>
<thead>
<tr>
<th>Days of Life</th>
<th>Water Output/Input Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Theophylline Group</td>
<td>Placebo Group</td>
</tr>
<tr>
<td>1</td>
<td>0.23 ± 0.18</td>
<td>0.71 ± 0.3</td>
</tr>
<tr>
<td>2</td>
<td>1.45 ± 0.11</td>
<td>0.36 ± 0.8</td>
</tr>
<tr>
<td>3</td>
<td>1.6 ± 0.55</td>
<td>0.92 ± 0.6</td>
</tr>
<tr>
<td>4</td>
<td>1.38 ± 0.6</td>
<td>1.7 ± 0.54</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Days of Life</th>
<th>Plasma Creatinine (mg/dL)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Theophylline Group</td>
<td>Placebo Group</td>
</tr>
<tr>
<td>1</td>
<td>1.0 ± 0.3</td>
<td>1.05 ± 0.4</td>
</tr>
<tr>
<td>2</td>
<td>0.97 ± 0.17</td>
<td>1.51 ± 0.41</td>
</tr>
<tr>
<td>3</td>
<td>1.02 ± 0.69</td>
<td>1.94 ± 1.1</td>
</tr>
<tr>
<td>4</td>
<td>0.89 ± 0.7</td>
<td>1.59 ± 0.7</td>
</tr>
<tr>
<td>5</td>
<td>0.71 ± 0.2</td>
<td>1.36 ± 0.9</td>
</tr>
</tbody>
</table>

- Bakr AF *Ped Neph* 2005; 20: 1249-1252
- Eslami Z et al. *AJN* 2005; 8: 222-6
Rasburicase

- **Rationale:** uric acid may play a pathogenic role in the development and progression of kidney disease

- **Outcomes:** retrospective review of 7 infants with AKI (SCr > 1.5 mg/dl) and UA > 8 mg/dl treated with single dose 0.15-0.2 mg/kg rasburicase

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Rasburicase improves hyperuricemia in infants with acute kidney injury

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*P<0.05
Whole body cooling

Rationale: may have protective effects in the setting of ischemia-reperfusion injury associated with asphyxiation

Outcomes: not systematically studied as an AKI prevention or treatment modality

- Neonatal network RCT – oligoanuria 21% hypothermic vs. 25% normothermic (NS) (Shankaran et al. NEJM 2005; 353: 1574-1584)
- CoolCap trial – AKI in 73/112 (65%) cooled vs. 83/118 (70%) controls (NS) (Gluckman et al. Lancet 2005; 365:663-670)
- TOBY trial (subset) – AKI in 3/12 (25%) cooled vs. 7/9 (78%) normothermic (p=0.03) (Roka et al. Acta Paediatr; 96: 1118-1121)
Fluid Is a Drug

- Old concept: give fluid to improve renal vascular flow and minimize azotemia

- How to Dose It?
  - Depends on fluid therapy phase
  - Response to the need for fluid vs. a non-fluid related symptom
    - Not all hypotension needs fluid
  - Has the patient already been overdosed?
Fluid management in AKI

- Fluid overload has been identified as an independent variable associated with increased mortality in pediatrics

Studies: (% FO and CRRT outcomes)
- Goldstein et al 2005 KI
- Foland et al 2004 CCM
- Gillespie et al 2004 Peds Neph
- Goldstein et al 2001 Pediatrics
- Adult studies as well- PICARD trial
Fluid is a drug

Rationale for initiating dialysis for fluid overload

– Allows for optimization of nutrition and provision of all necessary blood products
– Prevents further fluid and catabolic waste product accumulation
– Prevents progression of pulmonary edema and respiratory deterioration
– May prevent/decrease inadequate drug dosing due to unknown volume of distribution
– May shorten NICU/hospital length of stay
ppCRRT FO Threshold: Multivariate analysis

Mortality Rate

- ≤10% Fluid Overload: 22.1%, 29.4%
- 10%-20% Fluid Overload: 29.1%, 57.2%
- ≥20% Fluid Overload: 43.1%, 75.4%

Current Approaches to Renal Supportive Therapy and AKI

- Conservative management
- Non-dialytic interventions
- Renal replacement therapies
- New Concepts
Renal Support/Dialysis in Neonates

- Even with the best practices, this approach exposes the smallest children to added risk.
Figure 2: Pre-Filter CVVH

Hypotension Requiring...

96

no yes
Better Baby Dialysis Machines are coming!
Initiating RRT

CRRT

Access

Return

Replacement

Dialysate

Effluent

PD
TABLE 3. Factors independently associated with mortality in infants with acute kidney injury

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio</th>
<th>95% Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No AKI</td>
<td>Reference</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>AKI stage I</td>
<td>1.3</td>
<td>0.4–4.1</td>
<td>.70</td>
</tr>
<tr>
<td>AKI stage II</td>
<td>5.1</td>
<td>1.7–15.2</td>
<td>.004</td>
</tr>
<tr>
<td>AKI stage III</td>
<td>9.5</td>
<td>2.9–30.7</td>
<td>.0002</td>
</tr>
<tr>
<td>Single ventricle</td>
<td>2.6</td>
<td>1.1–6.2</td>
<td>.03</td>
</tr>
<tr>
<td>Circulatory support</td>
<td>7.0</td>
<td>1.8–28</td>
<td>.006</td>
</tr>
</tbody>
</table>

Model fit C statistic, 0.8. Patients without acute kidney injury were the reference group for these comparisons. AKI, Acute kidney injury.
Current Approaches to Renal Supportive Therapy and AKI

- Conservative management
- Non-dialytic interventions
- Renal replacement therapies
- **New Concepts**
  - AKI to CKD—why we are contributing to long term morbidity and healthcare costs
  - Biomarkers a new approach
  - Renal Angina
In utero

- Intrauterine growth retardation
  - Antenatal glucocorticoids
  - Antenatal medications
- Impaired nephrogenesis

Ex utero

- Hyperoxia
- Hypoxia
- Postnatal medications
- Immature kidney
  - Impaired nephrogenesis and glomerulogenesis
- Extrauterine growth restriction
  - Altered nutrition
  - Hormone, blood flow changes
- Nephron number
- Glomerular/tubular injury

Adulthood

Vulnerability to renal insult/damage
### Albuminuria:

<table>
<thead>
<tr>
<th>Author</th>
<th>Country of origin</th>
<th>Year of publication</th>
<th>Participant sex</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haymon</td>
<td>Australia</td>
<td>N/A</td>
<td>M &amp; F</td>
<td>0.95</td>
</tr>
<tr>
<td>Ramirezi</td>
<td>Singapore</td>
<td>2001</td>
<td>M &amp; F</td>
<td>1.02 (0.80, 1.37)</td>
</tr>
<tr>
<td>Rustberg</td>
<td>Sweden</td>
<td>1998</td>
<td>M &amp; F</td>
<td>1.56 (1.22, 1.99)</td>
</tr>
<tr>
<td>Vasarély</td>
<td>Hungary</td>
<td>2000</td>
<td>M &amp; F</td>
<td>2.00 (1.41, 2.83)</td>
</tr>
<tr>
<td>Yudkin</td>
<td>UK</td>
<td>2001</td>
<td>M &amp; F</td>
<td>1.40 (1.09, 1.79)</td>
</tr>
<tr>
<td>Nelson</td>
<td>USA</td>
<td>1998</td>
<td>M &amp; F</td>
<td>1.56 (1.33, 1.80)</td>
</tr>
<tr>
<td>Panelle</td>
<td>Netherlands</td>
<td>2000</td>
<td>M &amp; F</td>
<td>23.47</td>
</tr>
<tr>
<td>Hoy</td>
<td>Australia</td>
<td>1999</td>
<td>M &amp; F</td>
<td>15.26</td>
</tr>
<tr>
<td>Fagerholm</td>
<td>Finland</td>
<td>2000</td>
<td>M &amp; F</td>
<td>23.47</td>
</tr>
</tbody>
</table>

Subtotal (I-squared = 35.1%, p = 0.1):

- OR = 1.81 (1.19, 2.77)

### ESRD:

- OR = 1.58 (1.33, 1.88)

### Low eGFR:

- OR = 1.79 (1.31, 2.45)
Compared to Term (N=36), ELBW (N=64) were more likely to have:
- Smaller Renal Volumes at 7 and 11 years
- Higher Cystatin C
- Higher BUN levels
Rotterdam, The Netherlands ECMO program
423 neonates undergoing ECMO from 1992-2002
65% Incidence of AKI
Follow-up study at median age of 8.2 years
29% of neonates exposed to ECMO developed a sign of chronic renal injury

Children with RIFLE scores injury and failure 4.3 times higher odds of CKD signs or HTN
Follow-up of Acute kidney injury in Neonates during Childhood Years (FANCY): a prospective cohort study

Matthew W. Harer¹ · Chelsea F. Pope² · Mark R. Conaway³ · Jennifer R. Charlton⁴

• 34 VLBW infants follow up at 5 years of age
  • 20 with neonatal AKI and 14 without Neonatal AKI
• 9/34 (26%) had Cystatin C eGFR <90 mL/min/1.73 m² (p = 0.25)
  • 7/20 (35%) with AKI
  • 2/14 (14%) without AKI
• At least one sign of CKD (p< 0.05)
  • 13/20 (65%) with AKI
  • 2/14 (14%) w/o AKI

VLBW neonates with AKI had a 4.5 times greater risk of CKD
• Neonatal AKI is common in sick neonates in the NICU
• Those with AKI have worse outcomes, even after controlling for numerous potential confounders
• NICU graduates are at increased risk of CKD
  ▪ Conservative estimate of 5% of NICU admissions
  ▪ = 15,000 per year develop CKD in the United States
• Tons of work to be done.....
• This is truly an exciting time in the field of Neonatal Nephrology
Renal Angina
“Early” Recognition

Acute Kidney Injury (AKI)

Classic Risk Factors

Biomarkers

<table>
<thead>
<tr>
<th>Table 1. Risk factors for developing AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic and Clinical</td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Adults</td>
</tr>
<tr>
<td>age &gt; 65 years</td>
</tr>
<tr>
<td>diabetes</td>
</tr>
<tr>
<td>cirrhosis/hepatic failure</td>
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<tr>
<td>CHF</td>
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<tr>
<td>CKD</td>
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<tr>
<td>volume depletion</td>
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<tr>
<td>sepsis</td>
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<tr>
<td>cardiopulmonary bypass</td>
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<tr>
<td>exposure to nephrotoxins</td>
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<tr>
<td>Children</td>
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<tr>
<td>invasive mechanical</td>
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<tr>
<td>ventilation</td>
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<td>vasoactive medications</td>
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<td>nephrotoxic medications</td>
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<tr>
<td>sepsis</td>
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<tr>
<td>multiorgan failure</td>
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<tr>
<td>volume depletion</td>
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<tr>
<td>thrombocytopenia</td>
</tr>
<tr>
<td>hypoxia</td>
</tr>
<tr>
<td>neurologic dysfunction</td>
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<tr>
<td>stem cell transplant</td>
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</tbody>
</table>

Risk of Developing Acute Kidney Injury

Early Recognition

Early Treatment
(RRT, Medications)

Early Recovery

Conceptual Model for AKI

RENAL ANGINA

Current Point of Intervention

Creatinine rise

Normal → Increased risk → Damage → ↓ GFR → Kidney failure → Death/Recovery

Differential & Predictive Biomarkers

Diagnostic Antecedents Intermediate Stage Outcomes

Prognostic

New Point of Intervention
Thanks

- ppAKI consortium
- Stu Goldstein
- Tim Bunchman
- PICU & Nephrology staff
- Critical care teams