Neonatal Acute Kidney Injury: Outcome & Longterm implications

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Objectives

- Discuss problems with defining neonatal AKI (nAKI)
- Propose the question: Does nAKI lead to chronic kidney disease (CKD)?
- Detail early & late assessments & surveillance post nAKI
- Indicate future directions and research collaborations
AKI Definition Evolution

- >35 definitions of “acute renal failure” before 2000
  Kellum JA. *Curr Opin Crit Care* 2000
- 2004: **RIFLE** criteria created
  Bellomo R et al. *Crit Care* 2004
- 2007: Acute Kidney Injury Network (**AKIN**) criteria
- 2007: Pediatric (**pRIFLE**) criteria
- 2012: **KDIGO** classification
  *Kidney Int Supplements* 2012
- 2013: Neonatal modified KDIGO definition
Limited Literature on nAKI to CKD
Few Prospective & Longterm

- Anand SK J Pediatr 1978
- Shaw NJ Int J Cardiol 1991
- Marks SD J Pediatr 2005
- Abitbol CL Pediatr Nephrol 2003
- Bruel A Pediatr Nephrol 2016
- Harer MW Pediatr Nephrol 2017
- Maqsood S Pediatr Nephrol 2017
- Chaturvedi S Pediatr Nephrol 2017 (Review Article)
Issues with creatinine in the Neonate

- Interference with maternal creatinine
- Highly dynamic GFR in 1st few weeks of life
- Low muscle mass population
- Frequency of Cr monitoring varies from NICU to NICU
- What threshold of Cr rise should we use?
  - Historically, absolute SCr >1.5-2 mg/dL has been used
  - Are these thresholds too strict?
  - Should we be using lower %ΔSCr thresholds (pRIFLE, AKIN, KDIGO)?
Normal Trends in Neonatal Serum Creatinine

Is this AKI?
Proposes:

• A peak SCr >1.0 mg/dl with +/- the following:

• A delayed decline in SCr better defines AKI in the neonate.

• A nadir SCr <0.6 mg/dl by day 7.

pRIFLE criteria: AUC for mortality: 0.689, Addition of proposed U/O criteria increased to 0.886

<table>
<thead>
<tr>
<th>Table 6. Comparison between original and proposed pRIFLE criteria</th>
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<tbody>
<tr>
<td>Risk</td>
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<tr>
<td>------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Injury</td>
</tr>
<tr>
<td>Failure</td>
</tr>
<tr>
<td>Loss</td>
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<tr>
<td>End stage</td>
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</table>
Adding U/O Criteria Changes Incidence
AWAKEN Study

<table>
<thead>
<tr>
<th>Urinary or AKI status</th>
<th>Serum creatinine AKI status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Missing</td>
</tr>
<tr>
<td>Missing</td>
<td>140 (7%)*</td>
</tr>
<tr>
<td>Total</td>
<td>561 (28%)</td>
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</table>

Incidence with creatinine criteria: **380/2022 (19%)**
Incidence with Cr or U/O criteria: **605/2022 (30%)**

Figure 3: AKI (any stage) by urinary output and serum creatinine criteria (N=2022). Data are n (%). AKI=acute kidney injury. *Excluded from all calculations because of insufficient data for both urinary output and serum creatinine.

KDIGO vs AWAKEN: SCr Sequence

- KDIGO parameters may not distinguish AKI in neonates during the first week.
- Whereas, late follow-up may be required to pick up failure to “recover” from AKI with both.
Although the low gestational age group was the smallest number of the cohort, they had the highest incidence of AKI.
Acute kidney injury was recorded in the discharge summary for only 13.5% of 155 acute kidney injury survivors.

Seventy-five (16.5%) infants had multiple episodes of acute kidney injury.
Long-term follow-up of extremely low birth weight infants with neonatal renal failure

- Long term outcome of 20 ELBW infants with AKI
  - Peak SCr >2mg/dl > 48hrs and/or oliguria (<0.5 ml/kg/hr) after 3rd DOL
- Mean age at F/U: 7.5 +/- 4.6 yrs (range 3.2-18.5 yrs)
- Chronic renal impairment: eGFR <75 ml/min/1.73m²
- Also assessed for proteinuria (Urine PCR >0.2 mg/g), HTN (casual office BP), and renal size (U/S)
- 9/20 (45%) patients identified with low eGFR

Neonatal Renal Function: Progression of Renal Disease

• 20 LBW Preterm Infants with ARF in the Neonatal Period
• Average follow-up: 8±5 YRS
• 10 Developed chronic kidney disease (CKD)
• 10 Had recovery
• Initial Scr were similar at birth and improved at 1 year to <1.0 mg/dl.
• Urine pr/cr ratio was always more elevated in CKD patients.

Long-term follow-up of extremely low birth weight infants with neonatal renal failure

- Early proteinuria correlated to loss of kidney function.

- Persistent proteinuria correlated with progression of chronic kidney disease.

<table>
<thead>
<tr>
<th>Risk Index</th>
<th>Measure</th>
<th>Relative Risk</th>
<th>Sensitivity</th>
<th>PPV</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up/c @ 1 Year</td>
<td>&gt;0.6 mg/mg</td>
<td>∞</td>
<td>100%</td>
<td>75%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Scr @ 1 Year</td>
<td>&gt;0.6 mg/dl</td>
<td>5.0</td>
<td>75%</td>
<td>80%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI (kg/m²) Age % centile</td>
<td>&gt; 85%tile</td>
<td>5.3</td>
<td>89%</td>
<td>67%</td>
<td>0.03</td>
</tr>
<tr>
<td>Loss of Renal Mass</td>
<td>Renal US</td>
<td>1.3</td>
<td>67%</td>
<td>50%</td>
<td>0.60</td>
</tr>
<tr>
<td>Nephrocalcinosis</td>
<td>Renal US</td>
<td>1.1</td>
<td>22%</td>
<td>50%</td>
<td>1.00</td>
</tr>
</tbody>
</table>
ELBW & BMI: Components of Renal Disease Progression

- **Extreme Low Birth Weight** infants show renal disease progression with increased BMI.

CKD and Hypertension during Long-Term Follow-Up in Children and Adolescents Previously Treated with Extracorporeal Membrane Oxygenation

Alexandra J.M. Zwiers,* Hanneke IJsselstijn,* Joost van Rosmalen,* Saskia J. Gischler,* Saskia N. de Wildt,* Dick Tibboel,* and Karlien Cransberg†

- Rotterdam, Netherlands ECMO program
- 423 neonates undergoing ECMO from 1992-2002
- 65% Incidence of AKI (pRIFLE)
- Median age of follow-up: 8.2 years

GFR screening results for all patients stratified by age group.

Alexandra J.M. Zwiers et al. CJASN 2014;9:2070-2078
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 followed 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
- 4.5 times greater risk of CKD for VLBW neonates with AKI
- At least one sign of CKD (p< 0.05)
  - 13/20 (65%) with AKI
  - 2/14 (14%) w/o AKI

Harer MW et al. Pediatr Nephrol 2017
Many other factors associated with CKD in neonates

Chaturvedi S et al. Pediatr Nephrol 2017
Take Home Points

• Survivors of neonatal AKI may be at high risk of CKD
• Even without AKI, babies with LBW/IUGR and/or prematurity are at risk of CKD
• Long-term renal surveillance is needed
  • Nephrologists & neonatologists need to work together to make this happen
• What can “we” do for now?
  • Improve knowledge translation (spread the word)
  • Better recognition and recording of AKI episodes
  • Concentrate on AKI awareness & prevention
  • Design better larger scale prospective studies
Individualized CKD risk assessment upon follow up from the NICU:
* Prematurity <30 weeks
* History of AKI
* IUGR/SGA
* Structural abnormalities on renal ultrasound

LOWER RISK

With each Preventive Pediatric Health Care Visit

4-5 year old and adolescent visit:
- Serum creatinine
- Serum cystatin C
- Urine albumin/creatinine

Referred to Pediatric Nephrology

Sustained BP ≥95 percentile
- Microalbuminuria or proteinuria
- Elevated serum creatinine or cystatin C
- Abnormal renal ultrasound

HIGHER RISK

Blood pressure
- Growth parameters with BMI
- Counseling/Education

More frequent:
- Serum creatinine
- Serum cystatin C
- Urine albumin/creatinine

AKI
- Chronic disease
- Obesity
- Pre-hypertension