Neonatal Acute Kidney Injury

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Disclosures

• Consultation for AKI adjudication for Bioporto.

• Consultation for Travere

• Discuss off-label use of devices in children
Outline of the Presentation

• Brief review of Neonatal Kidney Function
• Definition of Neonatal AKI
• Risk factors, Epidemiology, and Outcomes of Neonatal AKI
• Evaluation and Management of Neonatal AKI
Newborn Renal Physiology
Neonatal Renal Physiology

• Nephrogenesis begins 5\textsuperscript{th} week – 34-36\textsuperscript{th} week
  • Implications for incidence and risk of CKD
• Significant changes in RBF after birth
  • Birth 2.5-4\% Cardiac Output
  • Adult 20-25\%
  • Result from: Increased systemic vascular resistance and decreased renal vascular resistance
    • Driven by Angiotensin II and Prostaglandins

Selewski et al. Pediatrics. 2015
Neonatal Renal Physiology: Tubular Function

• Limited Urinary Concentrating Ability
  • 400 mosmol/kg at birth to 1200 mosmol/kg at 1 year
  • Driven by
    • Decreased response to ADH
    • Poor solute gradients
    • Interference of PGE

• Tubules waste substances
  • Lower threshold for bicarb reabsorption
  • Glucose, Amino acids

• Sodium Reabsorption
  • Lower in neonates
  • Explains subtle changes in FeNa utilized in neonates
## GFR by Creatinine Clearance: 275 Preterm

| Preterm infants 0-3 days | Gestational Age | ml/min/1.3m² |
|--------------------------|-----------------|--------------|
| 27 weeks                 | 13              |
| 28 weeks                 | 16              |
| 29 weeks                 | 19              |
| 30 weeks                 | 22              |
| 31 weeks                 | 25              |
| Term                     | 26              |

| Preterm infants at 2 weeks | Gestational Age | ml/min/1.3m² |
|----------------------------|-----------------|--------------|
| 27 weeks                   | 16              |
| 28 weeks                   | 19              |
| 29 weeks                   | 22              |
| 30 weeks                   | 25              |
| 31 weeks                   | 28              |
| Term                       | 54              |

*** Classic Teaching: Adult GFR by age 2 ***

Vieux R et al. *Pediatrics*. 2010;125(5):e1186. Epub 2010 Apr 5
Normative SCr values by GA

Normal Creatinine (mg/dL) levels x gestational age

Rao, et al J of Den and Medical Science 2017
How should we define AKI using SCr

Gallini F: Pediatric Nephrology 2000 (15); 119-124
Acute Kidney Injury: Definition
Why do we need a definition?

• So we can all talk the same language....
• Compare studies
• Enrollment criteria for intervention studies
• So we can predict outcomes (Mortality, LOS, CKD)
• So we can identify AKI and **ACT** to improve outcomes when we see it
SCr-based definitions for AKI: Challenges

• Small changes in SCr are associated with mortality across populations
• SCr is a **DELAYED** surrogate of **FUNCTION** not **INJURY**
• SCr overestimates renal function due to tubular secretion of creatinine
• SCr varies by hydration status, sex, age, bilirubin level, medications
• 1\textsuperscript{st} postnatal week reflects maternal Cr
## 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 ≥ 0.3 mg/dl within 48 hrs or SCr rise ≥ 1.5- 1.9 X reference SCr* | > 0.5 and ≤ 1 ml/kg/hour |
| 2     | SCr rise ≥ 2 to 2.9 X reference SCr*              | > 0.3 and ≤ 0.5 ml/kg/hour |
| 3     | SCr rise ≥ 3 X reference SCr * or SCr ≥ 2.5 mg/dl or Receipt of dialysis | ≤ 0.3 ml/kg/hour |

*reference value is lowest previous value

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

Jetton et al, *The Lancet Child & Adolescent Health*, 2017
Acute Kidney Injury: Risk Factors, Epidemiology & Outcomes
Neonatal AKI

- Risk Factors For Neonatal AKI?
- How often does it happen?
- What are the outcomes in those with AKI?
## Varied Neonatal Populations

| Study            | Population                                | Definition                        | Incidence of AKI | Findings                                                                 |
|------------------|-------------------------------------------|-----------------------------------|------------------|--------------------------------------------------------------------------|
| Kaur et al, 2011 | Perinatal Asphyxia (n=36)                 | AKIN criteria                     | 41.7%            | AKIN capture AKI previously missed by previous standard of SCr > 1.5     |
| Selewski et al, 2013 | Perinatal Asphyxia (n=96)                  | Neonatal Modified KDIGO criteria  | 38%              | AKI predicted prolonged mechanical ventilation, length of stay, and abnormal brain MRI findings at 7-10 days of life |
| Zwiers et al, 2015 | Neonates on ECMO (N=242)                  | RIFLE                             | 64%              | Increased mortality in F group (65% mortality)                           |
| Criss et al, 2017 | Necrotizing Enterocolitis (N=281)         | Neonatal Modified KDIGO criteria  | 56%              | AKI is associated with increased mortality                               |
| Garg et al, 2021 | Necrotizing Enterocolitis (N=202)         | Severe AKI per Neonatal Modified KDIGO criteria | 32.6% | Severe AKI associated with: Surgical NEC, outborn, antenatal steroids, positive blood culture sepsis. |
## Varied Neonatal Populations

| Study                  | Population                                      | Definition      | Incidence | Findings                                                                                                                                 |
|------------------------|-------------------------------------------------|-----------------|-----------|------------------------------------------------------------------------------------------------------------------------------------------|
| Blinder et al, 2012    | Congenital Cardiac Surgery (N=430)               | AKIN            | 52%       | Severe acute kidney injury was associated:  
- Mortality and Length of MV  
All acute kidney injury stages associated with  
- Intensive care duration length of stay |
| Askenazi et al, 2013   | Sick near-term neonates (n=58)                   | Neonatal KDIGO criteria | 15.6%     | AKI associated with increased mortality and positive fluid balance                                                                      |
| Gohiya et al, 2021     | Sick near-term neonates (n=196)                  | Neonatal KDIGO criteria | 21%       | Mortality higher in those with stage 3 AKI  
AKI more common: HIE, Sepsis, Dehydration, Respiratory distress                                                                       |
| Mohamed et al, 2020    | Multicenter retrospective study PHIS (N=71621)    | Diagnostic codes | 3%        | Diuretic practices vary                                                                                                                |
| Coggins et al, 2020    | Late onset sepsis (N=203)                        | Neonatal KDIGO criteria | 20%       | AKI was independently associated with increased 30-day mortality                                                                     |
# Studies in Premature Infants 2014-2021

| Study             | Population                                      | Definition                              | Incidence of AKI | Findings                                                                                                                                                                                                 |
|-------------------|-------------------------------------------------|----------------------------------------|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Rhone et al, 2013 | Very Low Birth weight Infants (n=107)            | Neonatal Modified KDIGO criteria       | 26.2%            | AKI is associated with nephrotoxic medication exposure.                                                                                                                                                  |
| Carmody et al, 2014 | Very Low Birth weight Infants (n=455)          | Neonatal Modified KDIGO criteria       | 39.8%            | AKI associated with increased mortality and length of stay adjusted for severity of illness.                                                                                                             |
| Stoops et al, 2016 | Very Low Birth weight Infants (n=125)            | Neonatal Modified KDIGO criteria       | 30.5%            | Infants with AKI were more likely to have stage 2 IVH or higher than those without AKI.                                                                                                                  |
| Carmody et al, 2016 | Very Low Birth weight Infants (n=140)            | Neonatal Modified KDIGO criteria       | 25% in first week | Caffeine exposure was associated with decreased odds for AKI in logistic regression models                                                                                                                |
| Wu et al, 2021    | Systematic Review/ Meta-analysis, Low birthweight infants, 50 articles | Rate of AKI 25% | Patients with AKI had increased mortality (OR 7.13; 95% CI 5.91-8.6, p< 0.01)                                                                                                                  |
What are the outcomes in those with AKI? How often does it happen? What are the risk factors for neonatal AKI?
What Can We Do To Improve Outcomes?

Improving the quality of neonatal acute kidney injury care: neonatal-specific response to the 22nd Acute Disease Quality Initiative (ADQI) conference

| Table 1: Maternal Risk Factors for Neonatal AKI |
|------------------------------------------------|
| **Pre-Gestational** | **Gestational** | **Peripartum** |
| Socioeconomic factors | In vitro fertilization | Nephrotoxic medications |
| Age | Maternal Nutrition | Chorioamnionitis |
| Bodyweight | Alcohol consumption | Abruptio |
| Environmental stress | Smoking | Cord prolapse |
| Interpregnancy interval | Hypertensive disorders | Illicit drug use |
| CKD | Nephrotoxic medications | Perinatal asphyxia |
| Hypertension | Fetal growth restriction | |
Table 3: High-Risk Procedures & States

**High-Risk Procedures**
- Cardiopulmonary bypass
- Complex birth (or hemodynamic instability during birth)
- ECMO
- Radiologic studies and procedures utilizing iodinated contrast
- Major surgical procedures (NEC, CDH repair and Cardiac repair)
- Cancer treatment

**High-Risk States**
- Dehydration
- At risk for sepsis or culture-positive sepsis
- Necrotizing enterocolitis
- Decreased oncotic pressure
- Increased intra-abdominal pressure
- Hypotension requiring vasopressors
- High nephrotoxic medication exposure
- Hemodynamically significant PDA

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Table 2: High-Risk Neonates

| Population                      |
|--------------------------------|
| Preterm birth <28 weeks         |
| Small for gestational age       |
| Birth weight <1500 grams        |
| CAKUT                          |
| Congenital heart disease        |
| Undergoing cardiopulmonary bypass |
| Single ventricle physiology     |
| History of Heart transplant     |
| Extracorporeal membrane oxygenation (ECMO) |
| Hypoxic-ischemic encephalopathy |
Participating sites

• Criteria to join:
  • Volunteer to get data for AWAKEN
  • Have a Nephrologist and Neonatologist
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, Shanthy Sridhar, Craig S Wong, Juan C Kupferman, Russell L Griffin, David J Askenazi, on behalf of the Neonatal Kidney Collaborative (NKC)*

- The Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates (AWAKEN) study
  - 3 mo retrospective chart review of all NICU admissions
  - 24 centers
  - Main exclusion criteria: Neonates receiving ≤ 48 hours IVF

- 2022 neonates
  - 41% - ≥ 36 weeks Gestational Age
  - 45% - 29-36 weeks Gestational Age
  - 14% - < 29 weeks Gestational Age

Jetton and Askenazi, The Lancet Child & Adolescent Health, 2017
## Definition

| Stage | Serum creatinine | UOP over 24 hours |
|-------|------------------|-------------------|
| 0     | No change in serum creatinine or rise < 0.3 mg/dL | > 1 mL/kg/hour |
| 1     | SCr rise ≥ 0.3 mg/dL within 48 hours or SCr rise ≥ 1.5–1.9 X reference SCr* within 7 days | >0·5 and ≤ 1 mL/kg/hour |
| 2     | SCr rise ≥ 2 to 2.9 X reference SCr* | >0·3 and ≤0·5 mL/kg/hour |
| 3     | SCr rise ≥ 3 X reference SCr * or SCr ≥ 2.5 mg/dL** or Receipt of dialysis | ≤ 0·3 mL/kg/hour |

*Reference SCr is the lowest prior SCr measurement

** this is lower than the original KDIGO definition as a SCr of 2.5 mg/dl in neonates suggests a GFR < 10 ml/min/1.73m²

SCr=serum creatinine; UOP=urine output
Infants with AKI had higher mortality rate compared to those without AKI.

- AKI: 59/605 (9.7%) vs.
- NO AKI: 20/1417 (1.4%)

\[ p < 0.0001 \]

Jetton and Askenazi, *The Lancet Child & Adolescent Health*, 2017
AKI Incidence by GA

- **GA 22-29**
  - No AKI: 52%
  - AKI: 48%
  - Total: N=273

- **GA 29-36**
  - No AKI: 82%
  - AKI: 18%
  - Total: N=916

- **GA 36+**
  - No AKI: 63%
  - AKI: 37%
  - Total: N=833

Legend:
- Green: No AKI
- Red: AKI
- GA 22-29 (N=273)
- GA 29-36 (N=916)
- GA 36+ (N=833)
Outcomes by AKI status

| Parameter                        | Crude odds ratio or parameter estimate (95% CI) | p value   | Adjusted odds ratio or parameter estimate (95% CI) | p value   |
|----------------------------------|-----------------------------------------------|-----------|-----------------------------------------------|-----------|
| Mortality                        | 7.5 (4.5–12.7)                               | <0.0001   | 4.6 (2.5–8.3)*                                | <0.0001   |
| Length of stay (days)            | 14.9 (11.6–18.1)                             | <0.0001   | 8.8 (6.1–11.5)†                               | <0.0001   |

Crude odds ratios are presented for mortality and parameter estimates for length of stay. *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 length of stay adjusted for gestational age, birthweight, neonatal intubation, neonatal chest compression, admission for prematurity, admission for respiratory symptoms, admission for respiratory failure, admission for necrotising enterocolitis, admission for omphalocele, maternal multiple gestation, maternal use of non-steroidal anti-inflammatory drugs, neonatal height, neonatal head circumference, neonatal Apgar score at 5 min, and admission for other reasons.

Table 3: Prediction models for clinical outcomes

Jetton and Askenazi, *The Lancet Child & Adolescent Health*, 2017
Surveillance: You have to Look

Jetton and Askenazi, *The Lancet Child & Adolescent Health, 2017*

**Table 3. Center Characteristics (*median (25,75% IQR)*)**

| Site | Country | SCR Assay | SCR Count* | AKI Rate       |
|------|---------|-----------|------------|----------------|
| 1    | USA     | Enzymatic | 1 (1, 1)   | 2/80 (2.5%)    |
| 2    | USA     | Enzymatic | 1 (1, 1)   | 26/121 (21.5%) |
| 3    | India   | Jaffe     | 1 (1, 2)   | 11/53 (20.7%)  |
| 4    | USA     | Enzymatic | 1 (1, 3)   | 31/115 (27.0%) |
| 5    | USA     | Enzymatic | 1 (1, 3)   | 17/150 (11.3%) |
| 6    | Canada  | Jaffe     | 2 (1.5)    | 19/62 (30.6%)  |
| 7    | USA     | Enzymatic | 2 (1, 5)   | 21/103 (20.4%) |
| 8    | Canada  | Enzymatic | 3 (1, 7)   | 11/75 (14.7%)  |
| 9    | USA     | Enzymatic | 3 (1, 8)   | 46/77 (59.7%)  |
| 10   | USA     | Enzymatic | 3 (2, 7)   | 14/53 (26.4%)  |
| 11   | USA     | Enzymatic | 4 (2, 8)   | 20/137 (14.6%) |
| 12   | USA     | Jaffe     | 4 (2, 9)   | 13/69 (18.8%)  |
| 13   | USA     | Enzymatic | 4 (2, 12)  | 27/87 (31.0%)  |
| 14   | USA     | Enzymatic | 5 (2, 9)   | 29/67 (43.3%)  |
| 15   | USA     | Enzymatic | 5 (3, 8)   | 22/74 (29.7%)  |
| 16   | USA     | Both      | 6 (3, 10)  | 25/63 (39.7%)  |

*Cr surveillance varied by Institution*
Conclusions

• Incidence of Neonatal AKI using neonatal adapted KDIGO definition = 30%

• Neonates with AKI have 4.6 times higher odds of death

• Cr surveillance varied

• 14 manuscripts published from AWAKEN to date (www.babykidney.org)
Incidence, Risk Factors, and Outcomes of Neonatal Acute Kidney Injury: Protocol of a Multicentric Prospective Cohort Study [The Indian Iconic Neonatal Kidney Educational Registry]

Gopal Agrawal¹, Sanjay Wazir²*, Sidharth Kumar Sethi², Abhishek Tibrewal³, Rohan Dhir⁴, Naveen Bajaj⁵, Naveen Parkash Gupta⁴, Shishir Mirdunde⁴, Jagdish Sahoo⁶, Bineesh Balachandran⁷, Kamran Atzal⁷, Anubha Shrivastava⁸, Jyoti Bagla⁹, Sushma Krishnegowda¹⁰, Ananth Konapur¹¹, Kritika Soni¹², Vamsi Krishna Kolukula¹¹,¹², Rupali Jangid¹¹,¹², Timothy Bunchman¹⁹ and Rupesh Raina¹

• First prospective all cause neonatal AKI data repository in India

• Study:
  • This study is a multicentric, national, prospective cohort study [The Indian iconic Neonatal Kidney Educational Registry (TINKER)]
  • Conducted in level 2–3 NICUs in 11 centers across India.

• Aim:
  • Evaluate the incidence of neonatal AKI in NICUs in the country and
  • Determine the risk factors as well as the outcomes of such neonates—both short-term and long-term outcomes.

INCLUSION
Criteria: Neonates (≤ 28 days) who received intravenous (IV) fluids for at least 48 hours for hydration and/or nutrition

EXCLUSION
Criteria:
1. Neonates who died within 48 hours of admission
2. Presence of any lethal chromosomal anomaly, including Trisomy 13, 18 and anencephaly
3. Neonates requiring congenital heart surgery within the first 7 days of life
Evaluation and Management
Advances in Neonatal Acute Kidney Injury

Michelle C. Starr, MD, MPH, Jennifer R. Charlton, MD, MSc, Ronnie Guillet, MD, PhD, Kimberly Reidy, MD, Trent E. Tipple, MD, Jennifer G. Jetton, MD, Alisson L. Kent, BMBS, FRACP, MD, Carolyn L. Abitbol, MD, Namasivayam Ambalavanan, MD, Maroun J. Mhanna, MD, MPH, MBA, David J. Askenazi, MD, MSPH, David T. Selewski, MD, MS, Matthew W. Harer, MD, on behalf of the Neonatal Kidney Collaborative Board

DOI: 10.1542/peds.2014-3819 originally published online July 13, 2015;
What are the causes of SCr elevations in the neonates?

• Pre-renal — **FLUID RESPONSIVE**
• Intrinsic  
  • Nephrotoxic  
  • Ischemic  
  • Sepsis  
• Post Renal / Obstruction  
• “Chronic Kidney Disease”  
  • Congenital Anomalies  
  • Polycystic Kidney Disease  

• Although this framework provides a systematic approach:
  • IT DOES NOT POINT TO TREATMENT

• **NOT EVERYTHING PRERENAL NEEDS FLUID**
Causes of Pre-renal AKI

- Low blood volume
  - Perinatal blood loss
  - Hemorrhage
  - Dehydration
  - Transepidermal water loss
  - Poor intake
  - Gastric or Chest tube losses

- Low Intravascular volume
  - Capillary leak
  - Hydrops
  - Hypoalbuminemia

- Increased abdominal pressures
  - NEC
  - Abdominal Surgery
  - Ascites

- Poor cardiac output
  - Heart failure
  - Cardiac surgery

- Pharmacologic agents
  - Indomethacin/ Ibuprofen
  - ACE inhibitors
Pre-Renal in a Newborn

- The definition of fetal oliguria differs from older children
  - Needs to be further challenged
- Neonatal urine concentrating ability is immature (maximum concentration of 400 mosmol/kg)

| Test                              | Pre-renal AKI | Intrinsic AKI |
|-----------------------------------|---------------|---------------|
| Urine Sodium (meq/L)              | < 20-30       | >40           |
| Fractional excretion of sodium (FeNa) | <2%          | >2.5% (Term)  |
|                                   |               | > 3% (>31 weeks) ??? |
|                                   |               | > 6% (29-30 weeks) ??? |

Ishizaki, Acta Pedr. Jap. 1993
Intrinsic Neonatal AKI

• Ischemia
• Infections
  • Sepsis
  • Congenital infections
  • Pyelonephritis
  • Bacterial endocarditis
• Vascular causes
  • Renal artery thrombosis
  • Renal vein thrombosis

● Nephrotoxins
  ● Aminoglycosides
  ● Indomethacin
  ● Amphotericin B
  ● Radiocontrast dyes
  ● Myo / Hemoglobin
Nephrotoxic medication exposure in very low birth weight infants

Erika T. Rhone, J. Bryan Carmody, Jonathan R. Swanson & Jennifer R. Charlton

Journal of Maternal-Fetal & Neonatal Medicine.

• 107 VLBW infants survived to discharge from 4/2011 to 3/2012
• Nephrotoxins: acyclovir, amikacin, amphotericin B, gentamicin, ibuprofen, indomethacin, iohexol, tobramycin and vancomycin
• Most common: Gentamicin (86%), indomethacin (43%) and vancomycin (25%)
• AKI occurred in 28 (26.2%) infants
• Median number of nephrotoxic days was 8 d (IQR 3–21)
Baby NINJA (Nephrotoxic Injury Negated by Just-in-Time Action): Reduction of Nephrotoxic Medication-Associated Acute Kidney Injury in the Neonatal Intensive Care Unit

Christine Stoops, DO, MPH¹,², Sadie Stone, PharmD³, Emily Evans, PharmD⁴, Lynn Dill, RN²,³, Traci Henderson, RPh², Russell Griffin, PhD⁴, Stuart L. Goldstein, MD⁵,⁶, Carl Coghill, MD¹,², and David J. Askenazi, MD, MsPh¹,²,³

• Single Center QI project that occurred between 03/2015 and 09/2017

• High-risk NTX exposure criteria
  • 3 nephrotoxic medication within 24 hours
  • 4 calendar days of IV aminoglycoside

• Intervention
  • Daily serum creatinine (SCr) was obtained until 2 days after end of exposure or end of AKI

• Findings:
  • Reduction in exposures from 16.4 to 9.6 per 1000 patient-days (P = .03),
  • Reduction in percentage of nephrotoxic medication-AKI from 30.9% to 11.0% (P < .001)
  • Reduction in AKI intensity from 9.1 to 2.9 per 100 susceptible patient-days

Journal of Maternal-Fetal & Neonatal Medicine.
Management
Critical to management and intervention

- Is there a reversible cause?
- What is the GFR and Medication Dosing?
- What is the Fluid Balance?
- Electrolytes
- Blood Pressure
- Nutrition
Nutrition in Neonate with AKI

• Do not restrict protein or calories to prevent dialysis

• How long do you keep an oliguric baby undernourished to avoid further fluid overload?

• Remember that once you go on CRRT or PD, about 1 g/kg of protein will be lost per day
Interventions

• Loop Diuretics
  • May help convert to non-oliguric
  • KDIGO recommends **TIME LIMITED TRIAL**

• Dopamine
  • No definitive studies have demonstrated effect

• Theophylline/ Caffeine: Adenosine antagonist
  • Controlled studies showing benefit in asphyxiated newborns

• Fenoldopam : Dopamine agonist
  • No definitive studies have demonstrated effect
Theophylline & Caffeine

• Adenosine antagonists that prevent
  • Pre-glomerular vasoconstriction
  • Post-glomerular vasodilatation

• 6 randomized trials and metaanalysis have shown
  Theophylline increases GFR and urine output in:
  • Theophylline: Perinatal asphyxia (randomized trials)
  • Caffeine: Preterm neonates with RDS, Neonates with NEC
    (retrospective studies)
Treating perinatal asphyxia with theophylline at birth helps to reduce the severity of renal dysfunction in term neonates

Alok Raina¹, Aakash Pandita (aakash.pandita@gmail.com)¹, Rekha Harish⁵, Monika Yachha⁵, Ashu Jamwal¹

- Randomized controlled trial 159 neonates with perinatal asphyxia
  - No therapeutic hypothermia

- Receive a single dose of theophylline (5mg/kg) during first hour of life
  - Intervention: 78
  - Control: 81
Findings and Conclusions

• AKI
  • 15% in theophylline vs 48% in controls (p<0.01)

• Urine Output
  • Less oliguria in treated group
  • Better fluid balance over 3 days
Theophylline and aminophylline for prevention of acute kidney injury in neonates and children: a systematic review

Girish Chandra Bhatt,1 Priya Gogia,1 Martin Bitzan,2 Rashmi Ranjan Das3

► A single dose of adenosine antagonists reduces the incidence of AKI in term neonates with severe birth asphyxia by 60% without increasing the risk of complications (moderate quality evidence).

► Prophylactic theophylline given to neonates with severe birth asphyxia also decreases serum creatinine, maintains negative fluid balance and increases glomerular filtration rate.
3.7.1: We suggest that a single dose of theophylline may be given in neonates with severe perinatal asphyxia, who are at high risk of AKI. (2B)

Critical Remaining Question: Impact in those treated with therapeutic hypothermia.
Caffeine Exposure and Risk of Acute Kidney Injury in a Retrospective Cohort of Very Low Birth Weight Neonates

J. Bryan Carmody, MD, MPH¹, Matthew W. Harer, MD², Anna R. Denotti, MD³, Jonathan R. Swanson, MD, MS², and Jennifer R. Charlton, MD, MS⁴

• Caffeine is often used prophylactically for apnea of prematurity
• Retrospective chart review of 140 VLBW neonates
• Study sought to evaluate if caffeine exposure was protective against AKI (neonatal modified KDIGO)
Findings and Conclusion

• AKI occurred less frequently in the caffeinated
  • 17.8% vs 43.6% (p=0.002)

| Table III. Logistic regression models for AKI |
|-----------------------------------------------|
|                                               |
| n | Unadjusted | Fully adjusted | Final selected model |
|----|-------------|----------------|----------------------|
|    | OR (95% CI) | OR (95% CI)    | OR (95% CI)          |
|----|-------------|----------------|----------------------|
| 140| 0.28 (0.13-0.63) | 0.22 (0.07-0.75) | 0.21 (0.07-0.64) |
| 44 | 0.14 (0.04-0.53) | 0.06 (0.01-0.57) | 0.16 (0.03-0.89) |

• Conclusion: Those exposed to caffeine were less likely to experience AKI
Caffeine exposure and acute kidney injury in premature infants with necrotizing enterocolitis and spontaneous intestinal perforation

Noelia Aviles-Otero1 · Reeti Kumar2 · Dev Darshan Khalsa3 · Glen Green4 · J. Bryan Carmody5

Renal tissue oxygenation after caffeine administration in preterm neonates.
Harer, Matthew W; Rothwell, Amy C; Richard, Luke J; Adegboro, Claudette O; McAdams, Ryan M
ISSN: 0031-3998, 1530-0447; DOI: 10.1038/s41390-021-01579-3; PMID: 34006983
Pediatric research., 2021

Prediction of risk factors and outcomes of neonatal acute kidney injury
Kumail Algadeeb1 · Mostafa Qaraqel2 · Rahma Algadeeb3 · Hassan Faqeehi4 · Abdulrahman Al-Matary5
Renal Support Therapy
Indications for Renal Support Therapy

• Electrolyte (metabolic) imbalance
• Uremia with bleeding and or encephalopathy
  • Consider when BUN 80-100 (mg/dL)
• Nutritional support
• Intoxications, Inborn errors of Metabolism (IEM)
• Fluid Overload (hypervolemia with pulmonary edema/respiratory failure)
Peritoneal Dialysis

- Catheter
  - Soft tube
  - Surgical procedure or Acute catheter placement
  - Exit site critical
Peritoneal Dialysis - Advantages

• Daily waste and water removal
  • Usually less dietary and fluid restrictions
• Simple to learn and perform
• No blood access problems
• More daily flexibility
• Please see work by the Saving Young Lives group
  www.theisn.org/initiatives/saving-young-lives/
Peritoneal Dialysis - Disadvantages

- Peritoneal catheter
  - Pain
  - Infection
- Peritonitis
- Hernia risk
- Protein Loss

- **SLOW: VERY POOR IN METABOLIC CHILDREN (HYPERAMMONEMIA)**
Why CRRT?

• Allows for:
  • Precise Volume control/immediately adaptable
  • Uremic toxin removal

• Acid base balance
  • Rapid control of metabolic acidosis

• Electrolyte management
  • Control of electrolyte imbalances

• Allows for improved provision of nutritional support

• Management of sepsis/plasma cytokine filter
CRRT - Challenges

• Time consuming
• Resource intensive
• Access
• Anticoagulation
• Adult devices vs. Neonatal devices
The future: Aquadex

- Aquadex
  - Adapted adult SCUF machine
  - Pre-filter CVVH
  - ECV: 33 ml
  - Smaller lines
Carpediem

- Carpediem:
  - CRRT device designed for neonates: First case 2.9 kg, 65% FO, 25 days of therapy (Lancet 2014)
  - 22 Ga (4 French) catheter, BF 10 mL/min
  - Got approval for commercialization in the EU in 2013
  - Extracorporeal volume:
    - 27.2, 33.5, 41.5 ml ECV

Survival of infants treated with CKRT: comparing adapted adult platforms with the Carpediem™

Stuart L. Goldstein, Enrico Vidal, Zaccaria Ricci, Fabio Pagliaonga, Licia Peruzzi, Mario Giordano, Nicola Laforgia, Claudio Ronco

Pediatr Nephrol. 2021 Aug 20:1-9.
The future Newcastle Infant Dialysis and Ultrafiltration System (NIDUS)

• Novel system
  • Single Lumen Catheter
  • 9 cc extracorporeal volume
  • Driven by syringes and uncoupled the baby’s blood flow capacity from requirement of dialysis filter

• Promising results
  • Improved clearance in piglets (compared to PD)
  • Description of 10 babies

Coulthard et.al. Pediatric Nephrology 2014 29 (1873-1881)
Thank You
Questions?

My email: selewski@musc.edu

Neonatal Kidney Collaborative Website: www.babykidney.org
Revisiting the Definition
A new approach to define acute kidney injury in term newborns with hypoxic ischemic encephalopathy

Charu Gupta¹ · An N. Massaro²,⁴ · Patricio E. Ray¹,³,⁴

3 groups

1. Normal SCr trajectories

2. KDIGO AKI criteria

3. Delayed Scr clearance (but did not meet KDIGO AKI criteria)
   - Failed to increase eCrCl by >50 % or SCr ≤0.6 mg/dl by postnatal day 7
A new approach to define acute kidney injury in term newborns with hypoxic ischemic encephalopathy

Charu Gupta¹ · An N. Massaro²,⁴ · Patricio E. Ray¹,³,⁴

• Conclusion: “The rate of decline of SCr provides a sensitive approach to identify term newborns with AKI during the first week of life.”
• Took the 990 infants with
  • at least 1 SCr on days 1-2
  • at least 1 SCr on days 3-7
• Took the lowest SCr on days 1-2
• Took the highest SCr on days 3-7
• Determined the optimal absolute, percent, and maximum SCr thresholds that provide the highest mortality area under curve (AUC) and specificity for different GA groups

• Conclusion: Unique SCr rise cutoffs for different GA improves outcome prediction. Percent SCr rise does not add value to the neonatal AKI definition.