ERKNet
The European Rare Kidney Disease Reference Network

european society for paediatric nephrology

WELCOME TO

ESPN/ERKNet
Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Date: 07 April 2020

Topic: Neonatalogy: Neonatal Acute Kidney Injury

Speaker: David Selewski

Email: selewski@musc.edu

Moderator: Elena Levtchenko




musc Children's Health
Medical University of South Carolina

Neonatology: Acute Kidney Injury

musc Children's Health
Medical University of South Carolina

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Medical Director, Acute Dialysis Units
Medical University of South Carolina





Disclosures

- Consultation for adjudication for Bioporto.
- Discuss off-label use of devices in children

The Prospective Pediatric Acute Kidney Injury Research Group

KIDNEY INTERVENTIONS DURING MEMBRANE OXYGENATION

Neonatal KIDNEY Collaborative

NEPHRON
Neonatal and Pediatric Heart and Renal Outcomes Network

Outline of the Presentation

- Brief review of Neonatal Kidney Function
- What is AKI? What are the outcomes when it happens?
- How do you evaluate the neonate with acute kidney injury?
- How do you manage the newborn with AKI?

Newborn Renal Physiology

Neonatal Renal Physiology

- Nephrogenesis begins 5th week – 34-36th 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, Aminoacids
- Sodium Reabsorption
  - Lower in neonates
  - Explains subtle changes in FeNa utilized in neonates

GFR by Creatinine Clearance: 275 Preterm

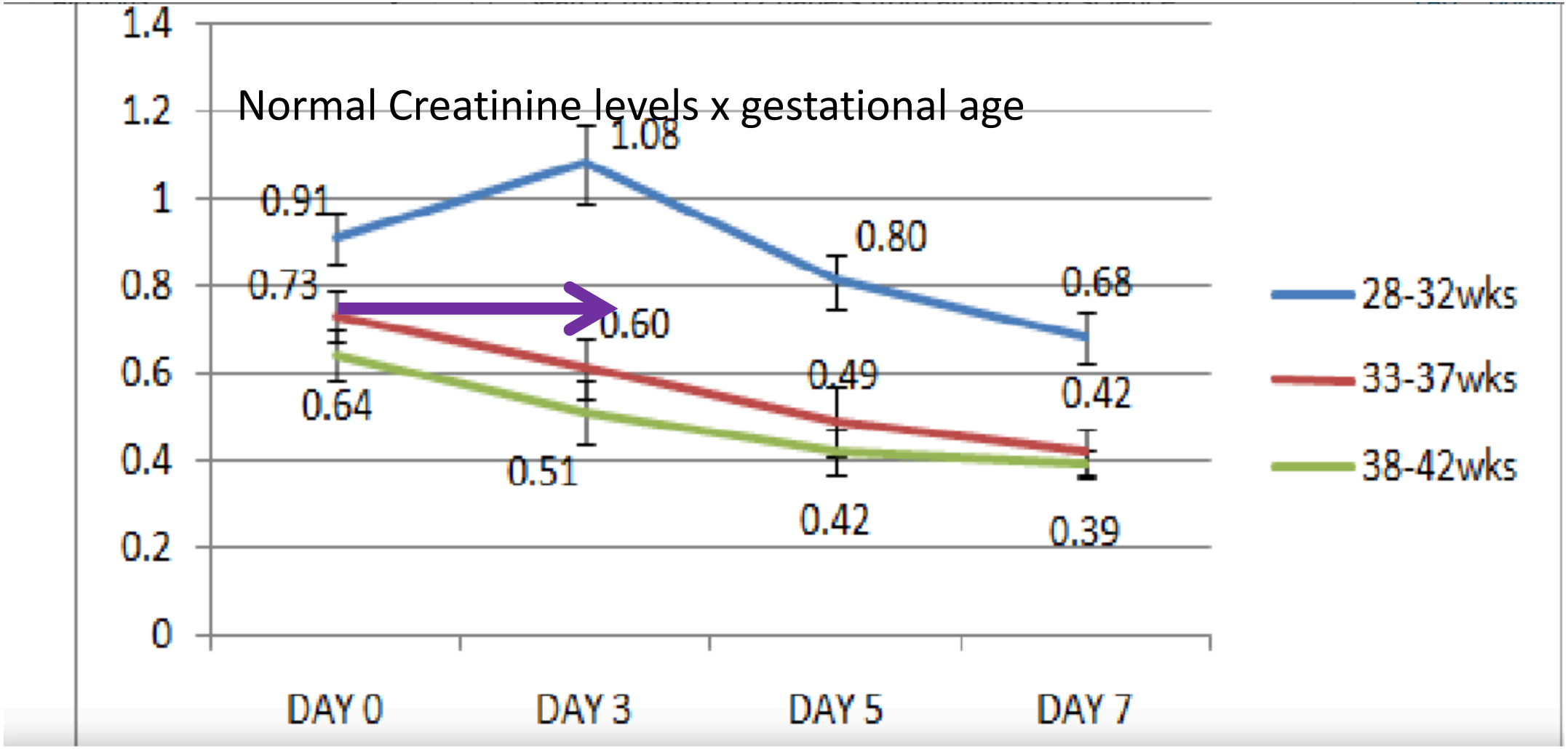
Preterm infants 0- 3days	
Gestational Age	ml/min/1.3m^2
27 weeks	13
28 weeks	16
29 weeks	19
30 weeks	22
31 weeks	25
Term	26

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

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

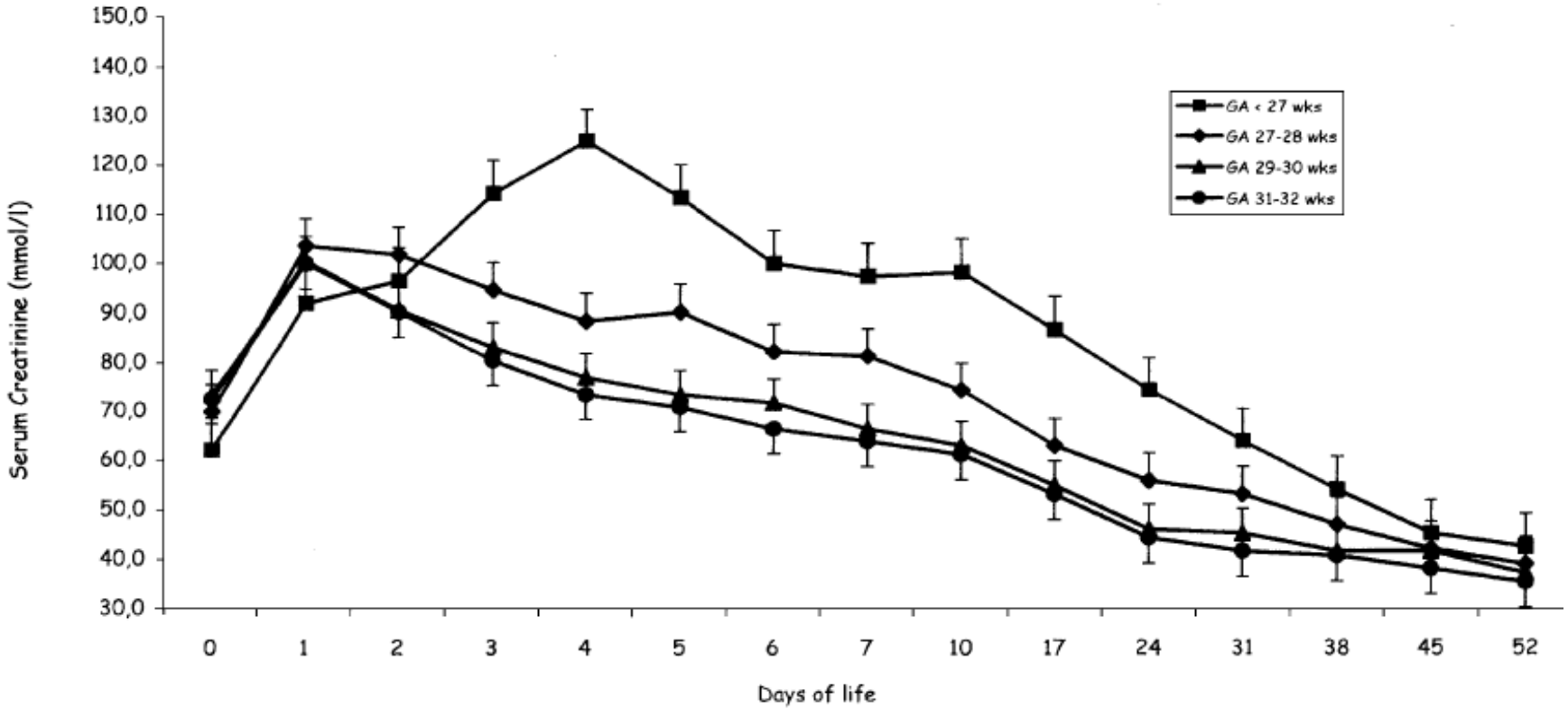
Vieux R et al. *Pediatrics*. 2010;125(5):e1186. Epub 2010 Apr 5

Normative SCr values by GA



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

Why do we need a definition?

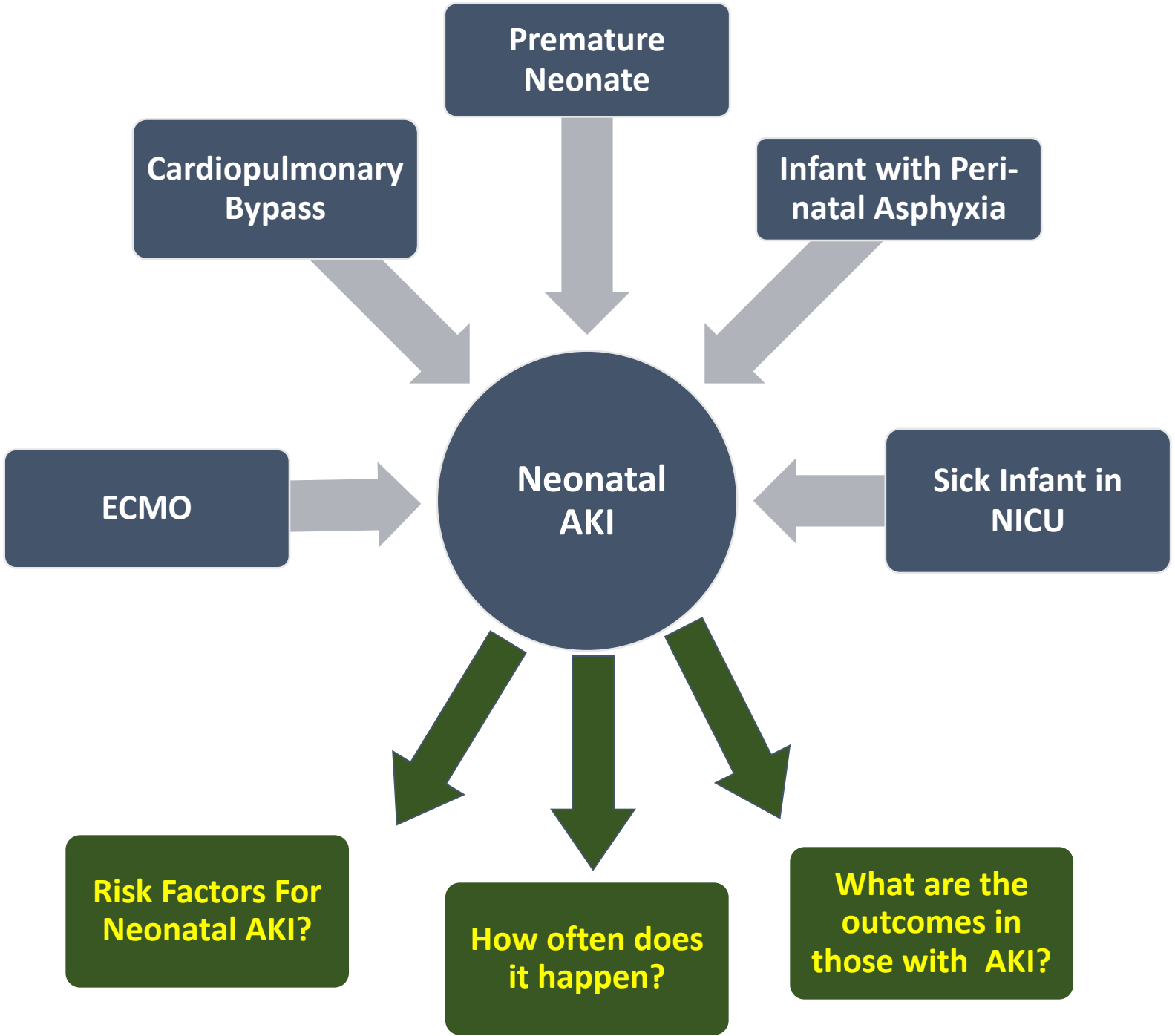
- So we can all talk the same language….
- Compare studies
- Enrollment criteria for intervention studies
- So we can predict something important
  - Mortality, LOS, CKD
- So we can ACT to improve when we see it

SCr-based definitions for AKI

- Small elevations of SCr are associated with mortality in numerous populations
- SCr is a surrogate of FUNCTION not INJURY
- SCr overestimates renal function due to tubular secretion of creatinine
- SCr varies by muscle mass, hydration status, sex, age, billirubin level, medications
- 1st 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)**		


Premature Neonate
Cardiopulmonary Bypass
Infant with Peri-natal Asphyxia
ECMO
Neonatal AKI
Sick Infant in NICU
Risk Factors For Neonatal AKI?
How often does it happen?
What are the outcomes in those with AKI?

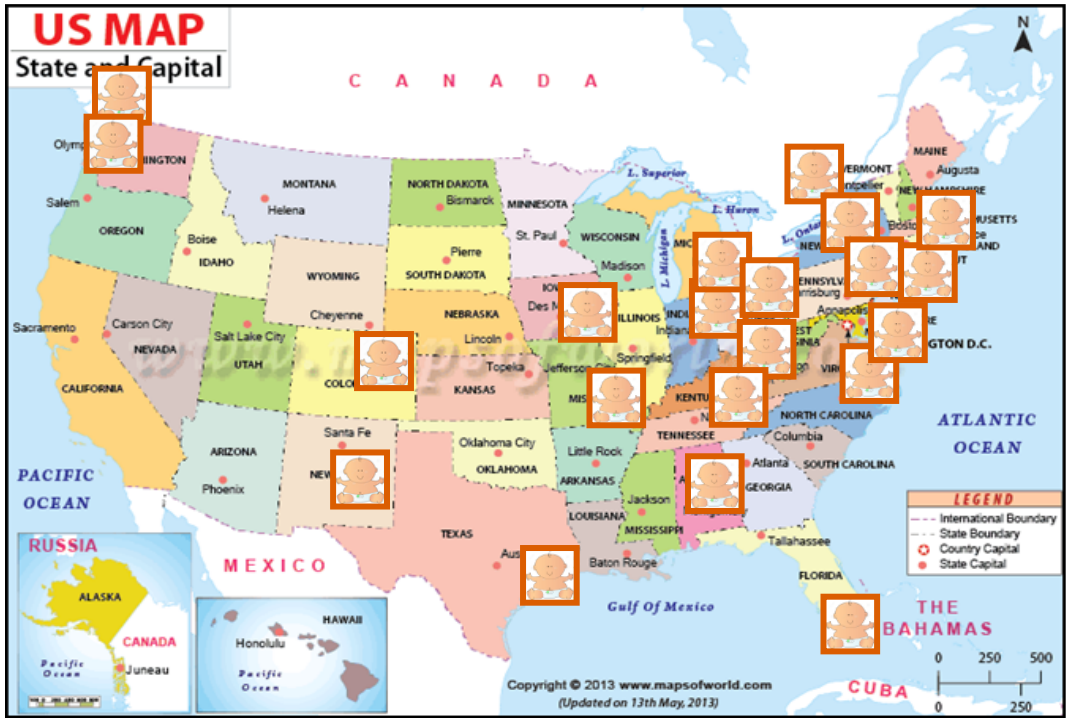
Varied Neonatal Populations

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 mg/dl
Askenazi et al, 2013	Sick near-term neonates (n=58)	Neonatal Modified KDIGO criteria	15.6%	AKI associated with increased mortality and positive fluid balance
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 Neonates with AKI had higher mortality (44% vs 25.6%, p = 0.008) and (HR 2.4, CI 1.2-4.8, p = 0.009)

Studies in Premies 2009-2014

Study	Population	Definition	Incidence of AKI	Findings
Askenazi et al, 2009	Very Low Birth weight Infants (n=195)	AKIN criteria	Matched case –control study	AKI is associated with increased mortality after adjustment for confounders
Koralkar et al, 2011	Very Low Birth weight Infants (n=229)	Neonatal Modified KDIGO criteria	18%	Adjusting for severity of illness AKI was associated with increased mortality
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

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 **A**ssessment of **W**orldwide **A**cute **K**idney injury **E**pidemiology in **N**eonates (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

e-Table 1. Definition of Acute Kidney Injury by Serum Creatinine and Urine Output

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

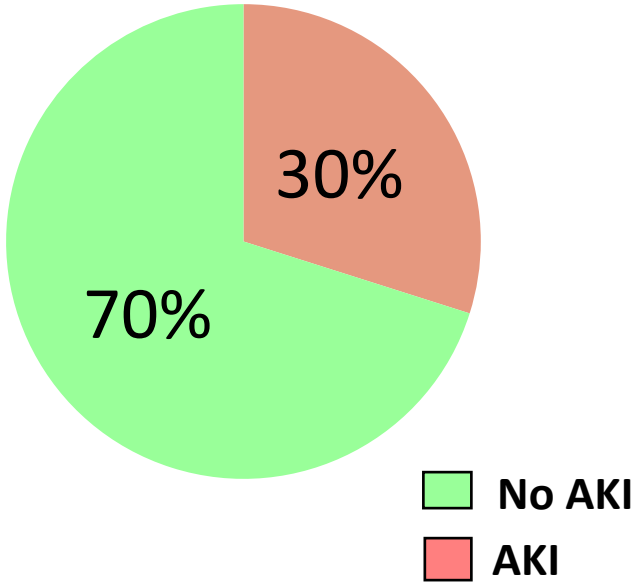
Jetton and Askenazi, *The Lancet Child & Adolescent Health, 2017*

AKI Outcomes in AWAKEN study

Enrolled Neonates

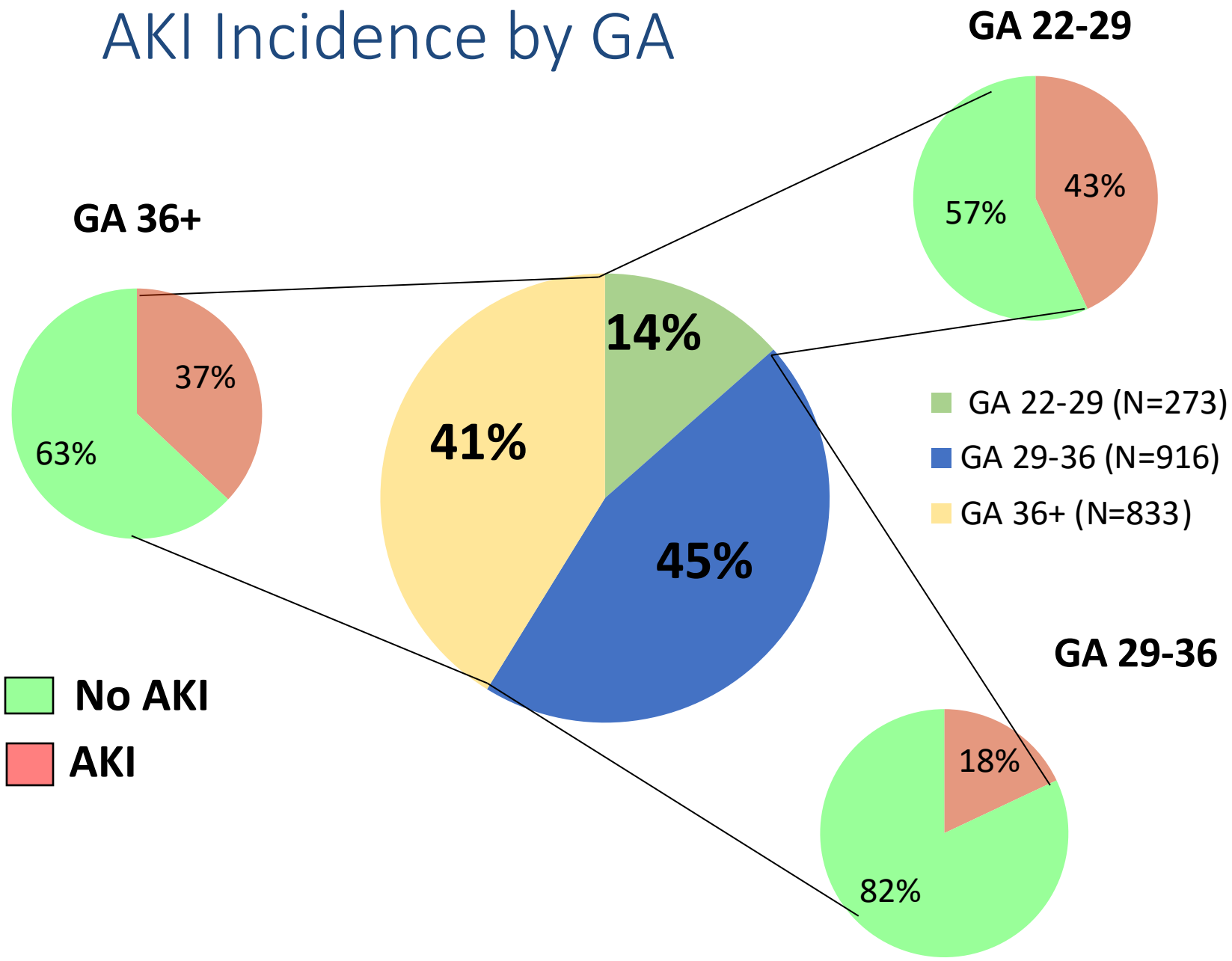
Infants with AKI had higher mortality rate compared to those Without AKI

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



Outcomes by AKI status

	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

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%)

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

Conclusions

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

- Neonates with AKI have 4.6 time higher odds of death

- **Cr surveillance varies**

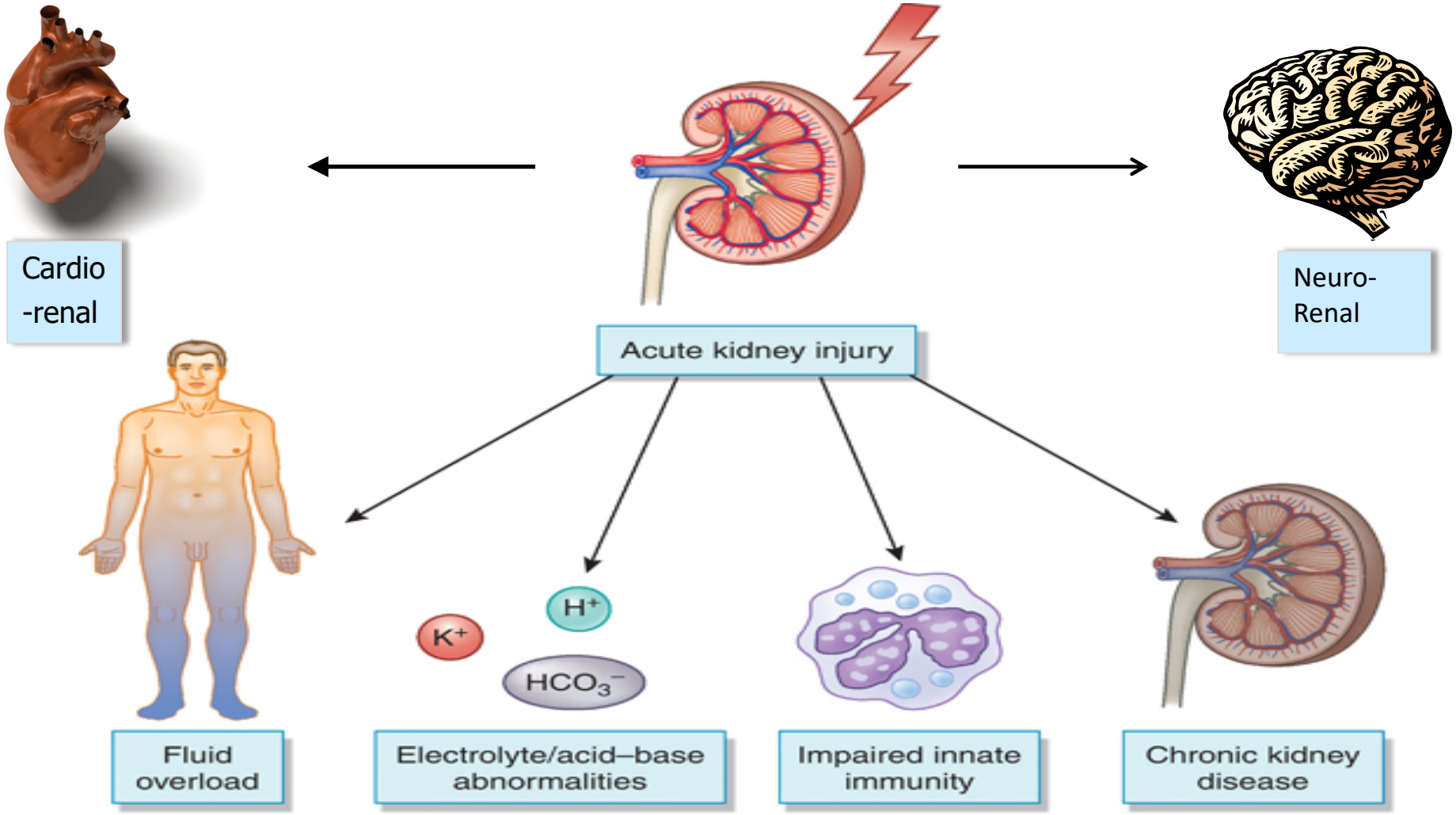
Acute Kidney Injury Guidelines Are Associated With Improved Recognition and Follow-up for Neonatal Patients

Katherine Vincent, NNP; Heidi J. Murphy, MD; Julie R. Ross, MD; Katherine E. Twombley, MD

- Retrospective cohort study of neonatal intensive care unit patients treated before guideline implementation and after
- Educational Intervention
- Conclusions:
  - Neonatal AKI guideline implementation was associated with improvements in recognition, diagnosis, and inpatient and outpatient nephrology consultation.

Vincent et al, Adv Neonatal Care. 2019 Sep 12

Its Not Just Mortality and Length of Stay



Relationship between acute kidney injury and brain MRI findings in asphyxiated newborns after therapeutic hypothermia

Subrata Sarkar[1], David J. Askenazi[2], Brian K. Jordan[1], Indira Bhagat[3], J.R. Bapuraj[4], Ronald E. Dechert[1] and David T. Selewski[5]

- Brain Imaging: At 7-10 days of life all infants treated with therapeutic hypothermia receive a brain MRI (blinded neuroradiologist)
  - Mildly abnormal: Lesions either in basal nuclei, or cortex
  - Severely abnormal: Injuries involved the basal ganglia/thalamus and cortex

- 88 of the 96 patients had MRI performed at a median of 8 days of life
  - 2 infants died prior to MRI, 6 infants had other imaging studies

- AKI was identified in 34 (39%) of neonate

- Brain MRI abnormalities related to hypoxia-ischemia was present in 50/88 (59%) neonates

- **AKI is independently associated with the presence of hypoxic-ischemic lesions on brain MRI**
  - **Adjusted OR = 2.9; 95% CI = 1.1-7.6**

Sarkar, Pediatr Res. 2014 Mar;75(3):431-5

Pediatric RESEARCH

www.nature.com/pr

CLINICAL RESEARCH ARTICLE

The impact of fluid balance on outcomes in critically ill near-term/term neonates: a report from the AWAKEN study group

David T. Selewski[1], Ayse Akcan-Arikan[2], Elizabeth M. Bonachea[3], Katja M. Gist[4], Stuart L. Goldstein[5], Mina Hanna[6], Catherine Joseph[7], John D. Mahan[8], Arwa Nada[9], Amy T. Nathan[10], Kimberly Reidy[11], Amy Staples[12], Pia Wintermark[13], Louis J. Boohaker[14], Russell Griffin[14], David J. Askenazi[14] and Ronnie Guillet[15] on behalf of the Neonatal Kidney Collaborative

Pediatric RESEARCH

www.nature.com/pr

CLINICAL RESEARCH ARTICLE

The impact of fluid balance on outcomes in premature neonates: a report from the AWAKEN study group

David T. Selewski[1], Katja M. Gist[2], Amy T. Nathan[3], Stuart L. Goldstein[4], Louis J. Boohaker[5], Ayse Akcan-Arikan[6], Elizabeth M. Bonachea[7], Mina Hanna[8], Catherine Joseph[9], John D. Mahan[10], Cherry Mammen[11], Arwa Nada[12], Kimberly Reidy[13], Amy Staples[14], Pia Wintermark[15], Russell Griffin[5], David J. Askenazi[5] and Ronnie Guillet[16] on behalf of the Neonatal Kidney Collaborative

Acute Kidney Injury and Bronchopulmonary Dysplasia in Premature Neonates Born Less than 32 Weeks' Gestation

Michelle C. Starr, MD[1,2] Louis Boohaker, MS[3] Laurie C. Eldredge, MD[4] Shina Menon, MD[2] Russell Griffin, PhD[5] Dennis E. Mayock, MD[6] Linzi Li, MPH[5] David Askenazi, MD[3] Sangeeta Hingorani, MD[2] on behalf of the Neonatal Kidney Collaborative

Acute Kidney Injury is Associated with Poor Lung Outcomes in Infants Born ≥32 Weeks of Gestational Age

Michelle C. Starr, MD[1,2] Louis Boohaker, MS[3] Laurie C. Eldredge, MD[4] Shina Menon, MD[2] Russell Griffin, PhD[5] Dennis Mayock, MD[6] David Askenazi, MD[3] Sangeeta Hingorani, MD[2] and on behalf of the Neonatal Kidney Collaborative

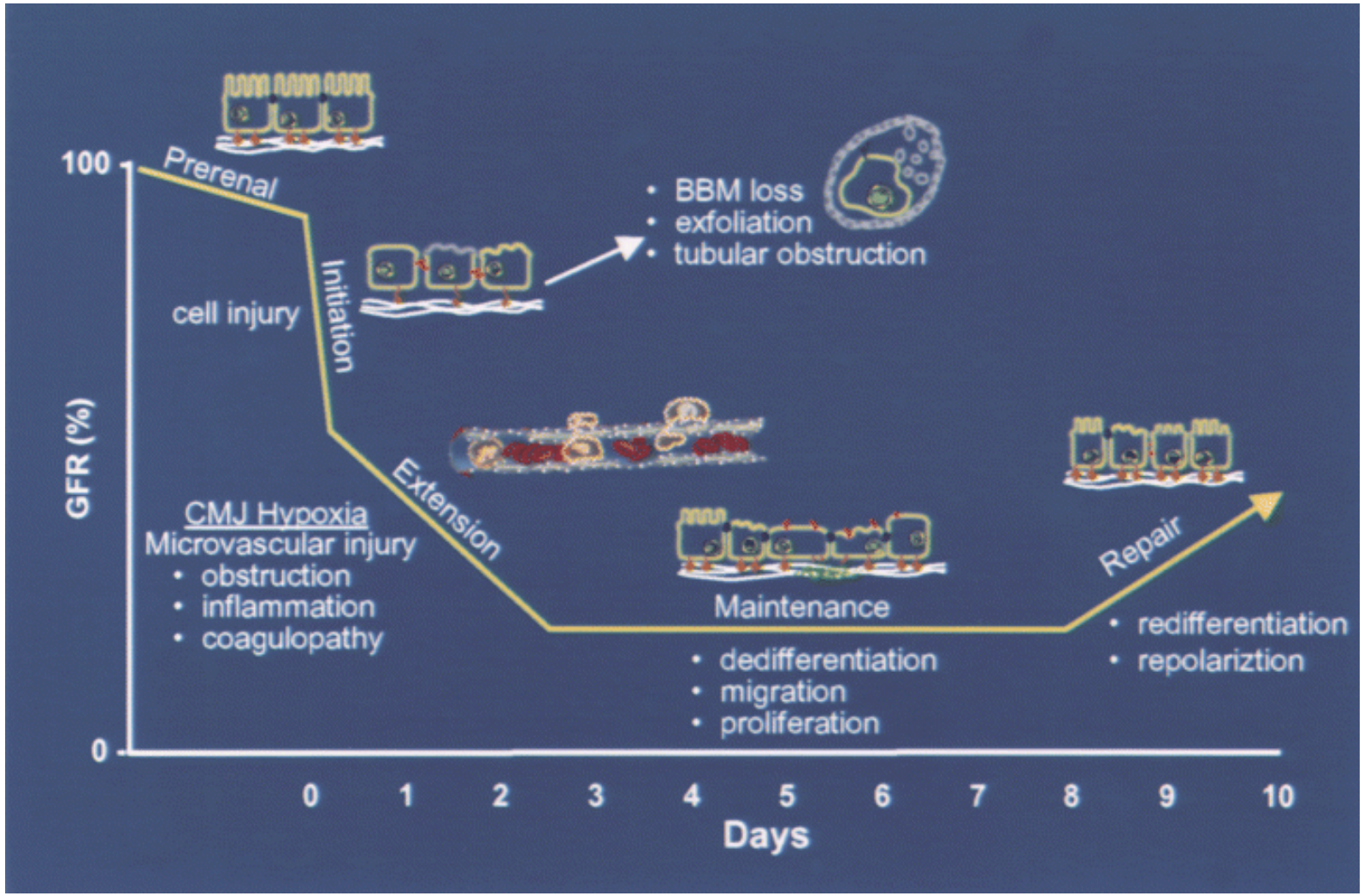
Etiology and Work-Up

What are the causes of SCr elevations in the newborn?

- 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**

Stages of Acute Kidney Injury



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

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)

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

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, MPH[1,2], Sadie Stone, PharmD[2], Emily Evans, PharmD[2], Lynn Dill, RN[2,3], Traci Henderson, RPh[2], Russell Griffin, PhD[4], Stuart L. Goldstein, MD[5,6], Carl Coghill, MD[1,2], and David J. Askenazi, MD, MsPH[1,2,3]

- 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

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

Management and Intervention

Critical to the evaluation, management, and intervention

- Is there a reversible cause?
- What is the Glomerular Filtration Rate?
- What is the Fluid Balance?
- How should I dose medications?
- 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

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
  - Adenosine dilates efferent arteriole and constricts afferent
  - Controlled studies showing benefit in asphyxiated newborns
- Fenoldopam : Dopamine agonist
  - Who knows

Theophylline & Caffeine

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

- 6 randomized trials and metanalysis have shown Theophylline increases GFR and urine output in:
  - Perinatal asphyxia (randomized trials)
  - Preterm neonates with RDS (retrospective studies)

ACTA PÆDIATRICA
NURTURING THE CHILD

Acta Pædiatrica ISSN 0803-5253

REGULAR ARTICLE

Treating perinatal asphyxia with theophylline at birth helps to reduce the severity of renal dysfunction in term neonates

Alok Raina[1], Aakash Pandita (aakash.pandita@gmail.com)[1], Rekha Harish[1], Monika Yachha[2], Ashu Jamwal[1]

- 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
- Remaining Question: Impact in those treated with therapeutic hypothermia

ISSN: 1476-7058 (Print) 1476-4954 (Online) Journal homepage: https://www.tandfonline.com/loi/ijmf20

Effectiveness of theophylline administration in neonates with perinatal asphyxia: a meta-analysis

Ioannis Bellos, Aakash Pandita & Monika Yachha

To cite this article: Ioannis Bellos, Aakash Pandita & Monika Yachha (2019): Effectiveness of theophylline administration in neonates with perinatal asphyxia: a meta-analysis, The Journal of Maternal-Fetal & Neonatal Medicine, DOI: 10.1080/14767058.2019.1673722

The Journal of Maternal-Fetal & Neonatal Medicine, 2019

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*)

KDIGO AKI GUIDELINES, 2012

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Caffeine Exposure and Risk of Acute Kidney Injury in a Retrospective Cohort of Very Low Birth Weight Neonates

J. Bryan Carmody, MD, MPH[1], Matthew W. Harer, MD[2], Anna R. Denotti, MD[3], Jonathan R. Swanson, MD, MS[2], and Jennifer R. Charlton, MD, MS[4]

- 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

		Unadjusted	Fully adjusted*			Final selected model†		
	n	OR (95% CI)	OR	Tolerance	NNE	OR	Tolerance	NNE
All patients	140	0.28 (0.13-0.63)	0.22 (0.07-0.75)	0.78	2.93	0.21 (0.07-0.64)	0.90	2.87
Prolonged invasive respiratory support	44	0.14 (0.04-0.53)	0.06 (0.01-0.57)	0.74	4.33	0.16 (0.03-0.89)	0.91	5.02

- Conclusion: Those exposed to caffeine were less likely to experience AKI

Research

JAMA Pediatrics | Original Investigation

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)

Indications for Renal Support Therapy

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

Dialysis for Neonates: A Series of Challenges

- Equipment designed for bigger people
- No specific protocols
- Complications may be magnified
- No clear guidelines
- Limited outcome data
- Small patient with small blood volume
  - Blood Prime Critical

Fluid Overload and Mortality in Children Receiving Continuous Renal Replacement Therapy: The Prospective Pediatric Continuous Renal Replacement Therapy Registry

Scott M. Sutherland, MD,[1] Michael Zappitelli, MD, MSc,[2] Steven R. Alexander, MD,[1] Annabelle N. Chua, MD,[3] Patrick D. Brophy, MD,[4] Timothy E. Bunchman, MD,[5] Richard Hackbarth, MD,[5] Michael J.G. Somers, MD,[6] Michelle Baum, MD,[6] Jordan M. Symons, MD,[7] Francisco X. Flores, MD,[8] Mark Benfield, MD,[9] David Askenazi, MD,[9] Deepa Chand, MD,[10] James D. Fortenberry, MD,[11] John D. Mahan, MD,[12] Kevin McBryde, MD,[13] Douglas Blowey, MD,[14] and Stuart L. Goldstein, MD[3]

AJKD, June 2010.

- 297 children from 13 centers
- Patients with 20% fluid overload at CRRT initiation had an adjusted mortality OR of 8.5 (95% CI, 2.8-25.7)

P<0.05

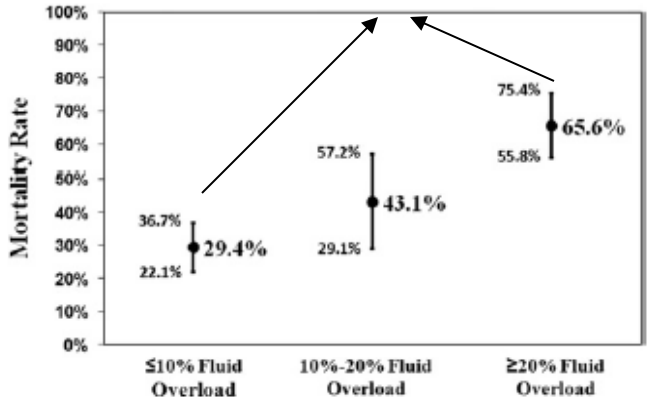


Figure 1. Mortality rates of pediatric intensive care unit patients receiving continuous renal replacement therapy subdivided by degree of fluid overload. Error bars represent 95% confidence intervals for the mortality rate in each fluid overload group. There was a statistically significant difference in mortality among the 3 groups. Patients with ≥ 20% fluid overload had significantly higher mortality than patients with < 10% fluid overload and those with 10%-20% fluid overload. Patients with 10%-20% fluid overload had a trend toward increased mortality compared with patients with < 10% fluid overload; however, this trend did not reach statistical significance ($P = 0.07$).

How do you define fluid overload in the NICU?

Pediatric RESEARCH

www.nature.com/pr

CLINICAL RESEARCH ARTICLE

The impact of fluid balance on outcomes in critically ill near-term/term neonates: a report from the AWAKEN study group

David T. Selewski[1], Ayse Akcan-Arikan[2], Elizabeth M. Bonachea[3], Katja M. Gist[4], Stuart L. Goldstein[5], Mina Hanna[6], Catherine Joseph[7], John D. Mahan[8], Arwa Nada[9], Amy T. Nathan[10], Kimberly Reidy[11], Amy Staples[12], Pia Wintermark[13], Louis J. Boohaker[14], Russell Griffin[14], David J. Askenazi[14] and Ronnie Guillet[15] on behalf of the Neonatal Kidney Collaborative

- First 7 postnatal Days
- 3870 potential days in 645 neonates
  - 74.3% of days complete intake and output data.
  - A weight was available on 80.5% of days

Pediatric RESEARCH

www.nature.com/pr

CLINICAL RESEARCH ARTICLE

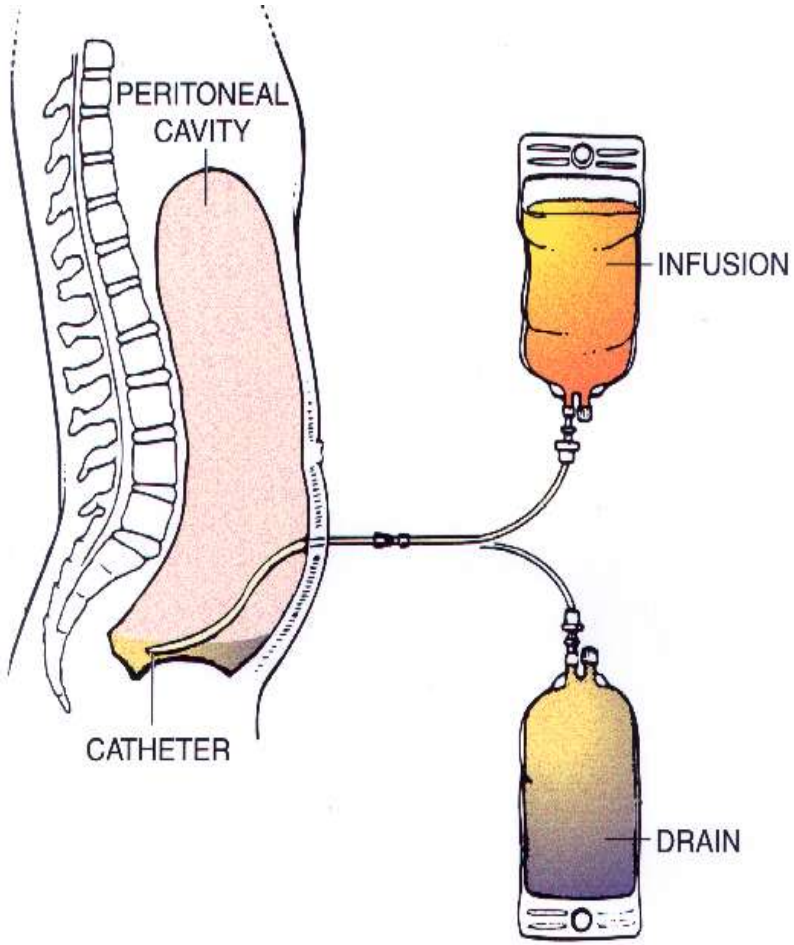
The impact of fluid balance on outcomes in premature neonates: a report from the AWAKEN study group

David T. Selewski[1], Katja M. Gist[2], Amy T. Nathan[3], Stuart L. Goldstein[4], Louis J. Boohaker[5], Ayse Akcan-Arikan[6], Elizabeth M. Bonachea[7], Mina Hanna[8], Catherine Joseph[9], John D. Mahan[10], Cherry Mammen[11], Arwa Nada[12], Kimberly Reidy[13], Amy Staples[14], Pia Wintermark[15], Russell Griffin[5], David J. Askenazi[5] and Ronnie Guillet[16] on behalf of the Neonatal Kidney Collaborative

- First 7 postnatal Days
- 6042 potential days in 1007 neonates
  - 71.9% of days complete intake and output data.
  - A weight was available on 90.9% of days

ANSWER: WEIGHT

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

Peritoneal Dialysis - Disadvantages

- Peritoneal catheter
  - Pain
  - Infection
- Peritonitis
- Hernia risk
- Protein Loss
- **SLOW: VERY POOR IN METABOLIC CHILDREN (HYPERAMMONEMIA)**

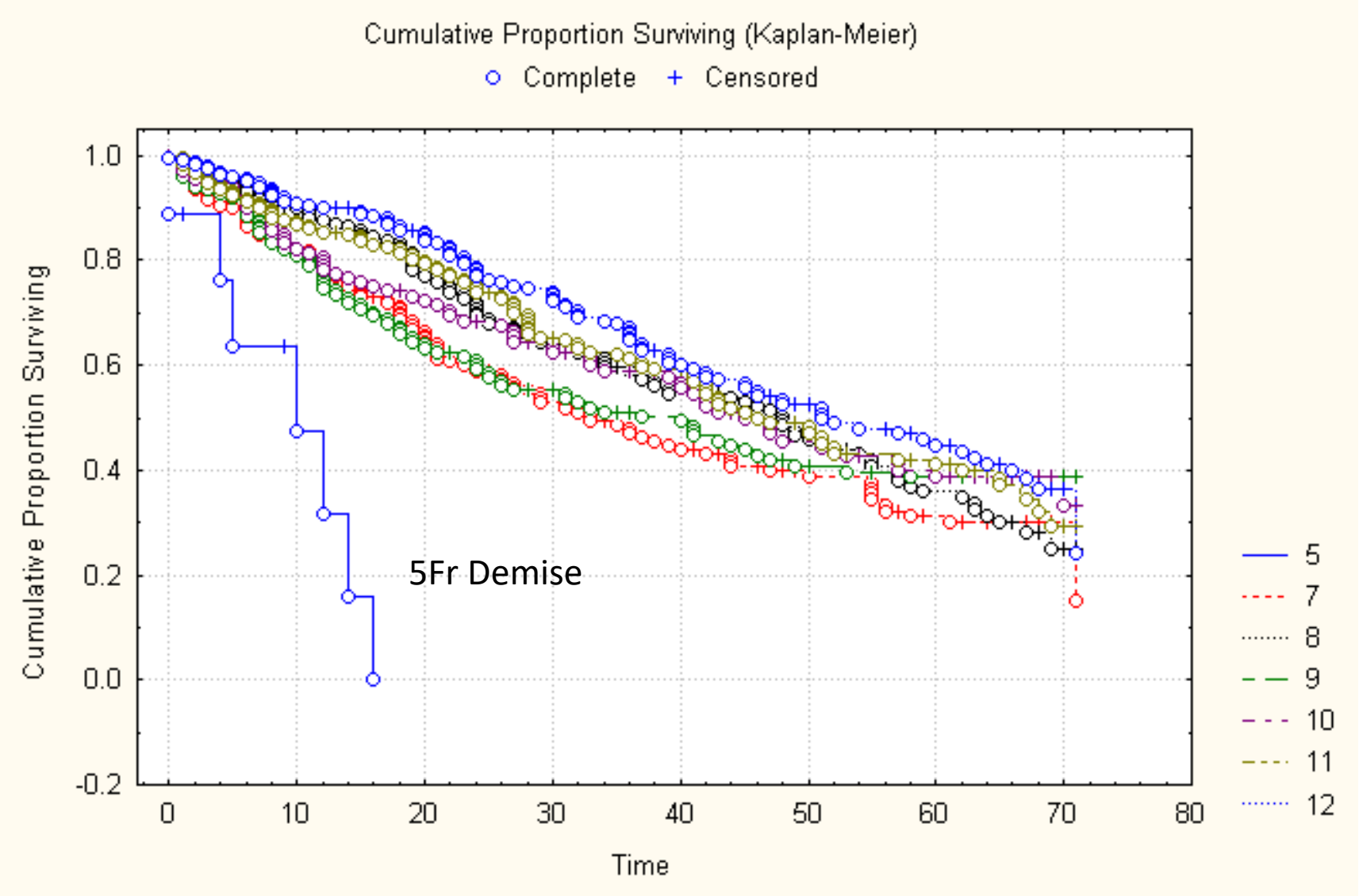
Why CRRT?

- Reduces hemodynamic instability preventing secondary ischemia
  - Precise Volume control/immediately adaptable
  - Uremic toxin removal
  - Effective control of uremia, hypophosphatemia, hyperkalemia
- 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
- Safer for patients with head injuries

CRRT access: Why does it matter?

- Access function is crucial for therapy
- Flows obtained will affect adequacy of blood flow for dose delivered and can affect filter-circuit life
- Downtime from clotted circuits-access is time off therapy

Circuit Survival Curves by French Size of Catheter



Hackbarth R et al: *IJAIO* December 2007

The future: Aquadex

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

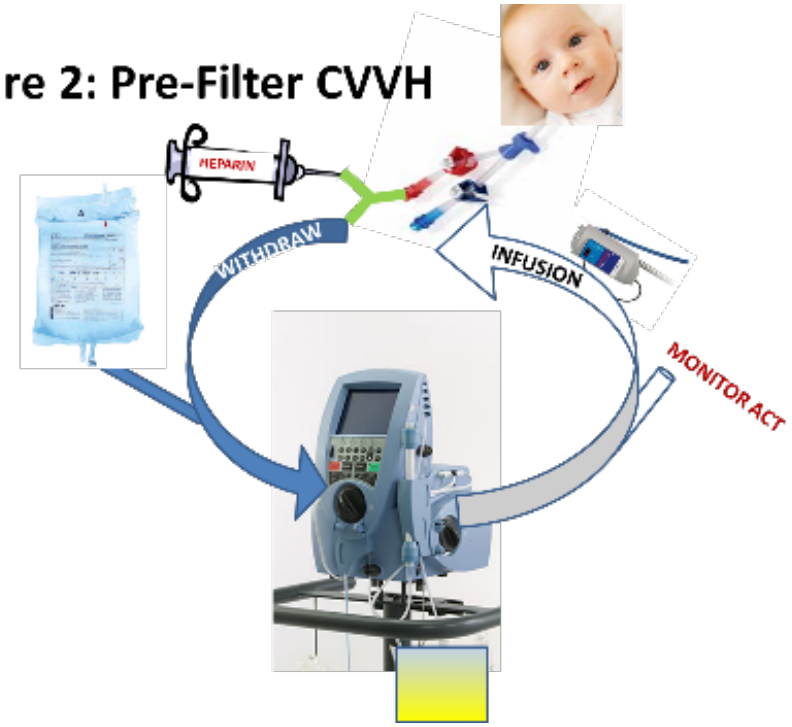
CJASN
Clinical Journal of American Society of Nephrology

Kidney Support in Children using an Ultrafiltration Device

A Multicenter, Retrospective Study

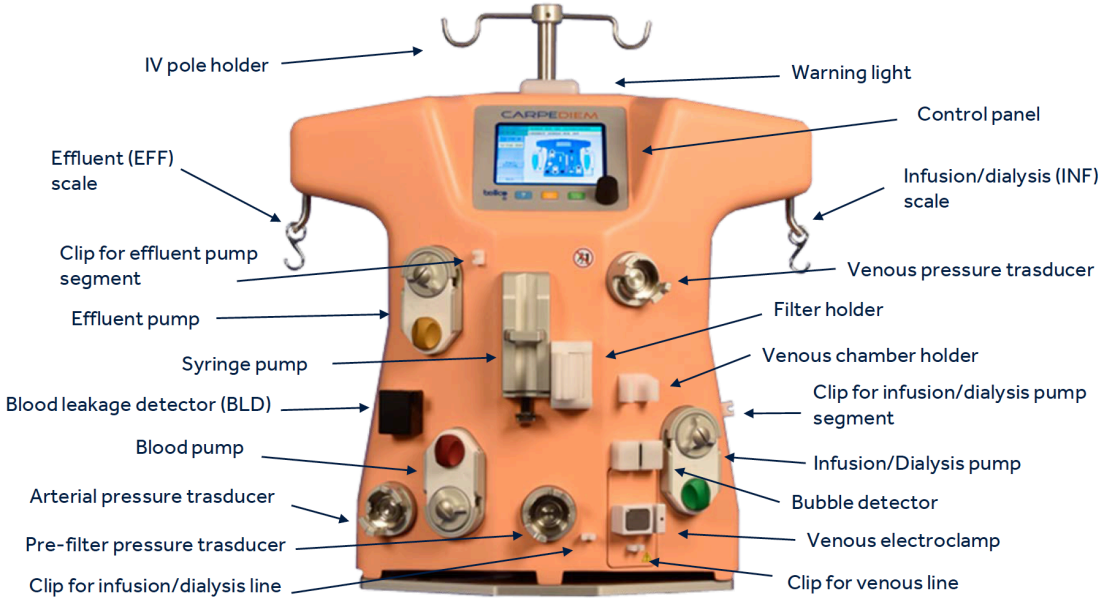
Shina Menon,[1] John Broderick,[2,3] Raj Munshi,[1] Lynn Dill,[4] Bradley DePaoli,[2] Sahar Fathallah-Shaykh,[4] Donna Claes,[2,3] Stuart L. Goldstein,[2,3] and David J. Askenazi[4]

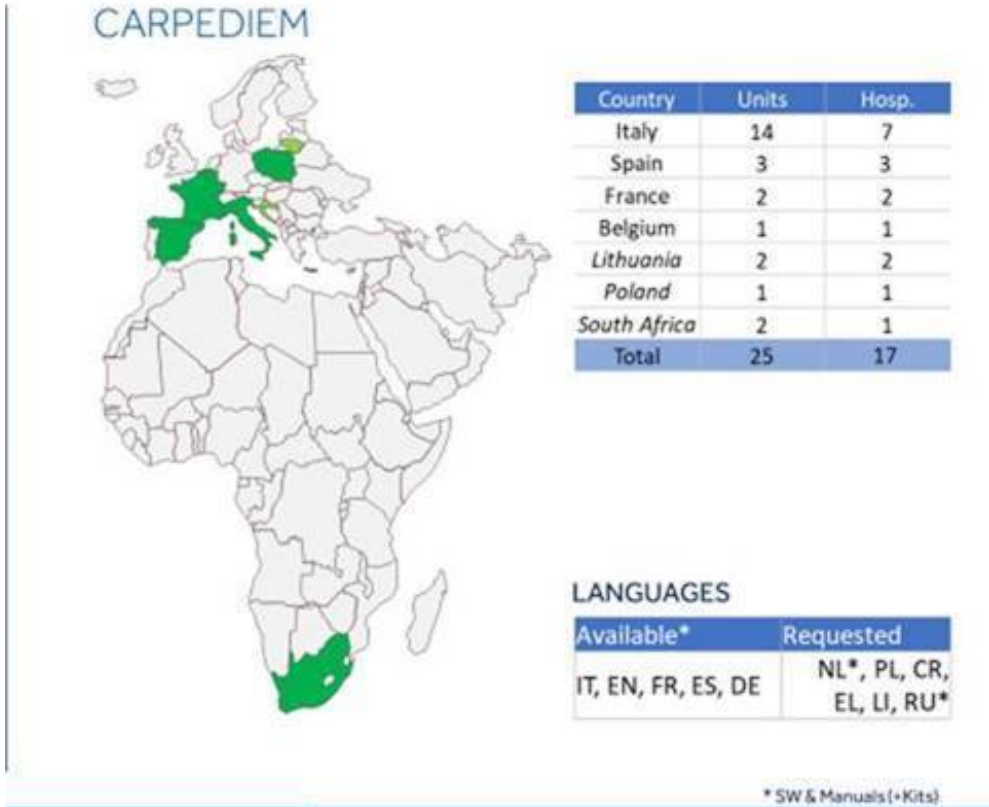
Figure 2: Pre-Filter CVVH



The future: Carpediem

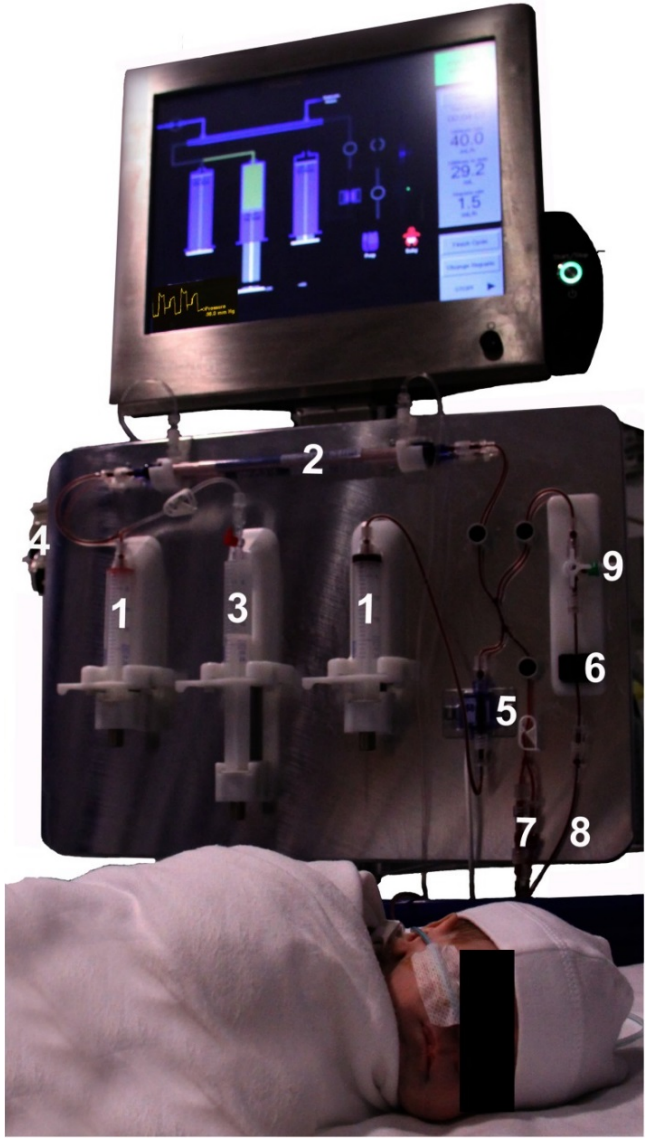
- Carpediem:
  - CRRT device designed for neonates: First case 2.9 kg, 65% FO, 25 days of therapy (Lancet 2014)
  - 22 Ga (4 French) catheter, BF 10 mL/min
  - Got approval for commercialization in the EU in 2013
  - Extracorporeal volume:
    - 27.2, 33.5, 41.5 ml ECV





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)

- **Question 1: Maternal history: 38 year old. EGA 41+3/40. Two hours prior to delivery non-reassuring fetal monitoring with expedited forceps delivery for a fetal bradycardia for 10 minutes. Apgar scores 1 at 1 minute. Intubated and resuscitated. Arterial cord gas: pH 6.9, and Lactate 13. Neonate met criteria for cooling for Hypoxic Ischaemic Encephalopathy. At 96 hours of age he remains oliguric/anuric and his weight is 3300 grams (>20% fluid overload and Cr is 600µmol/L (6.8 mg/dL)).**

Questions?

Next Webinars

IPNA Clinical Practice Webinars

Date: **16 April 2020**

Speaker: **Joseph Flynn**

Topic**: Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents**

ERKNet Advanced Webinars on Rare Kidney Disorders

Date: **28 April 2020**

Speaker: **Bertrand Knebelmann**

Topic: **Cystinuria**

ESPN/ERKNet Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Date: **05 May 2020**

Speaker: **Max Liebau**

Topic: **ARPKD**

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