Management of Acute Kidney Injury in the Neonate

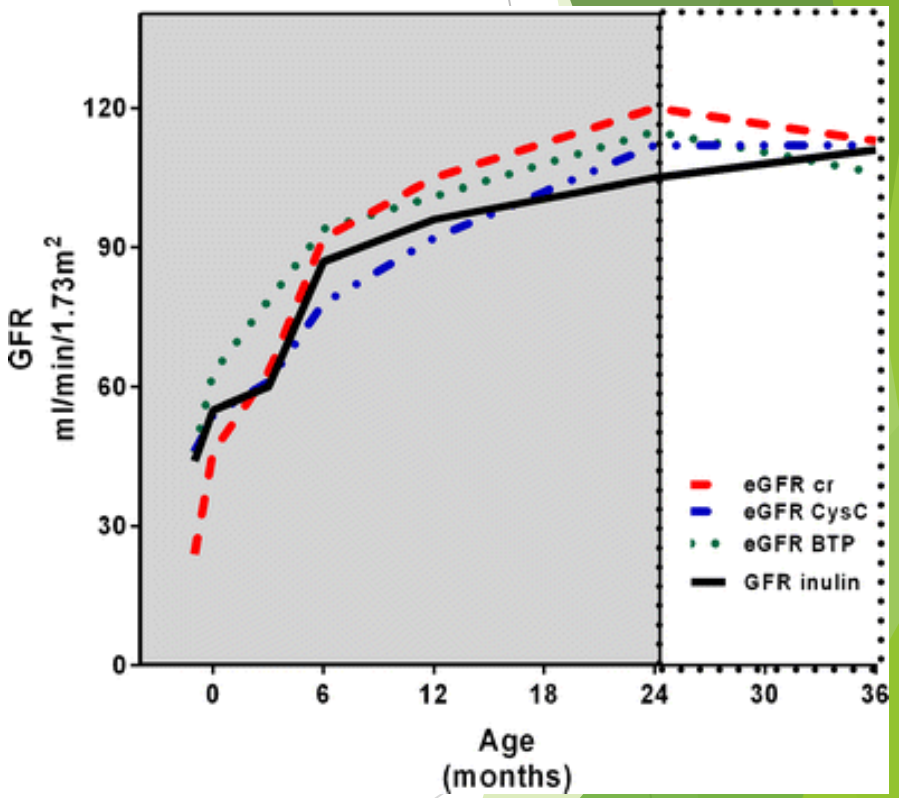
Carolyn Abitbol, M.D.
University of Miami Miller School of Medicine
/ Holtz Children's Hospital

Objectives

- Summarize the dilemmas in diagnosing & recognizing AKI in neonates
- Provide a paradigm for diagnosis and assessment
- Review medical treatment options
- Review available renal replacement options

Maturation of Kidney Function:birth to 2 years

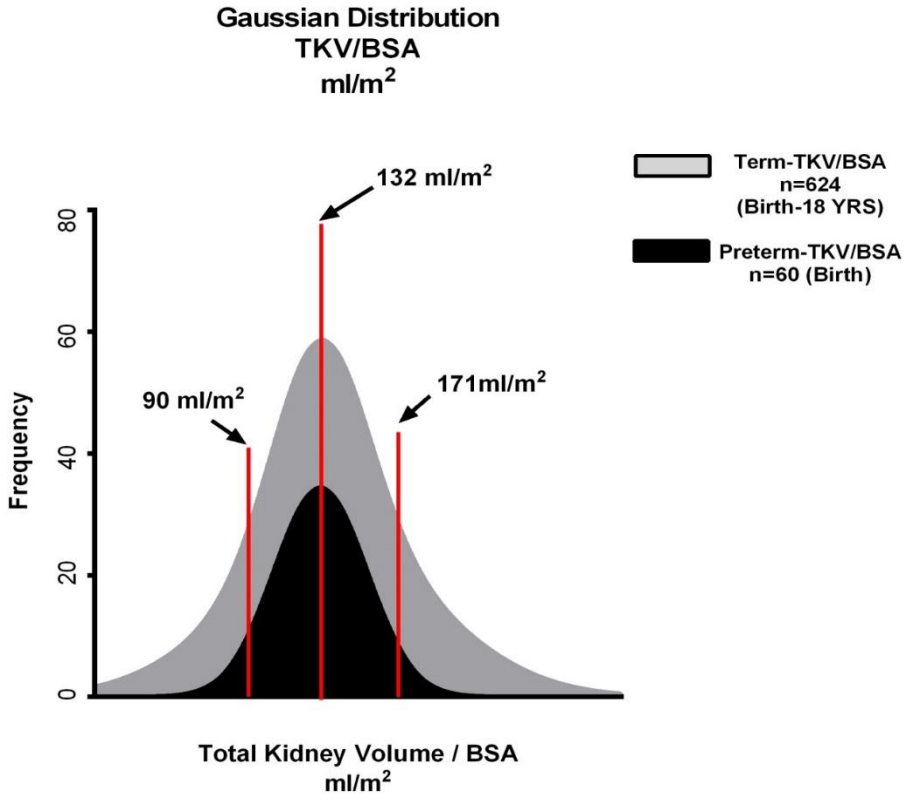
	Preterm	Term	3 MOS	6 MOS	12 MOS	24 MOS	36 MOS
SCr mg/dl	0.7±0.3	0.5±0.1	0.4±0.2	0.3±0.2	0.3±0.1	0.3±0.2	0.3±0.2
ScysC mg/L	1.4±0.2	1.3±0.2	1.2±0.3	1.0±0.2	0.9±0.2	0.7±0.1	0.7±0.1
GFR_{INULIN} $ml/min/1.73m^2$	44±9	55±8	60±17	87±22	96±12	105±17	111±19
$eGFR_{cr}$ $ml/min/1.73m^2$	24±7	46±10	63±8	92±10	105±12	120±17	113±10
$eGFR_{cysC}$ $ml/min/1.73m^2$	46±10	54±8	61±10	78±8	92±12	112±10	112±8
$eGFR_{TKV/cysC}$ $ml/min/1.73m^2$	54±8	58±9	63±17	75±6	84±20	107±16	107±16

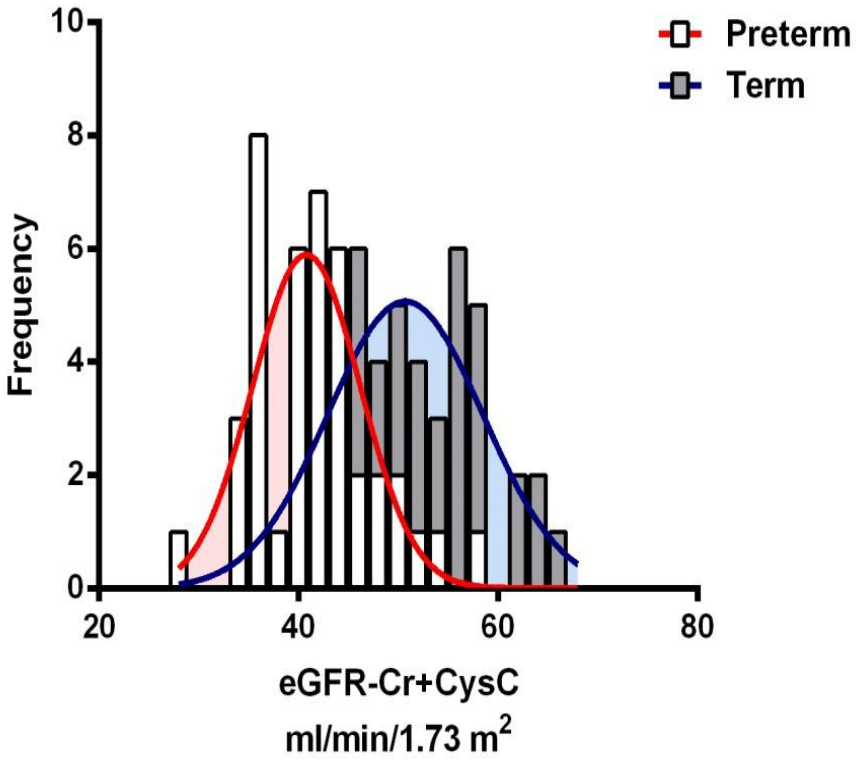


Neonatal Kidney Size and Function in Preterm Infants: What Is a True Estimate of Glomerular Filtration Rate?

Carolyn L. Abitbol, MD[1], Wacharee Seeherunvong, MD[1], Marta G. Galarza, MD[2], Chryso Katsoufis, MD[1], Denise Francoeur, RN[1], Marissa DeFreitas, MD[1], Alcia Edwards-Richards, MD[1], Vimal Master Sankar Raj, MD[1], Jayanthi Chandar, MD[1], Shahnaz Duara, MD[2], Salih Yasin, MD[3], and Gaston Zilleruelo, MD[1]

J Pediatr 2014;164:1026-31





eGFR = GA + MAP + TKV

Supported by the Gerber Foundation

Endogenous Markers of GFR

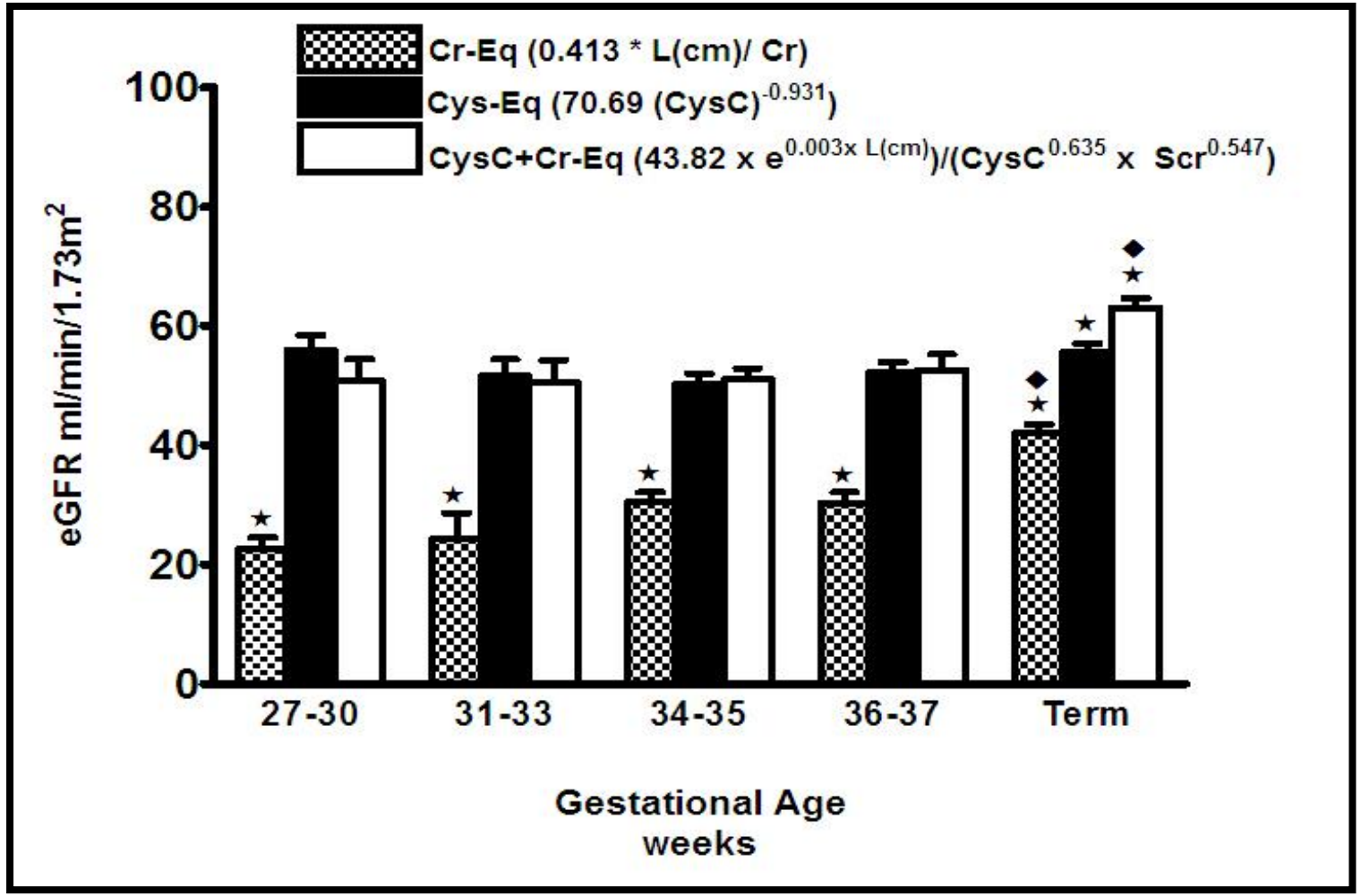
Cystatin C

- Small molecular weight protein: cysteine protease inhibitor
- Filtered by the glomeruli & totally reabsorbed & metabolized by the proximal tubules.
- Does not appear in the urine except for tubular injury.
- Cost $10-$15

Creatinine

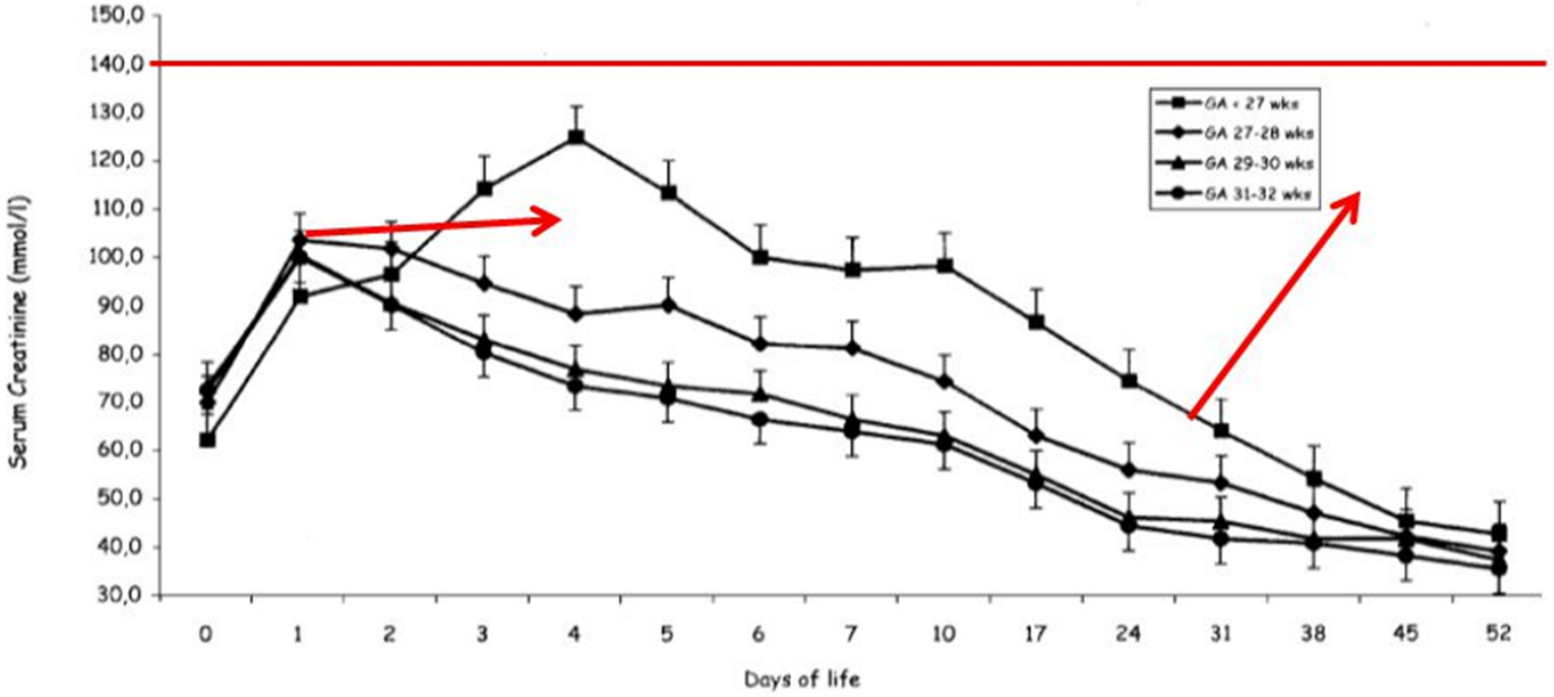
- Endogenous product of creatine (muscle breakdown)
- Filtered by glomeruli but also ***secreted & reabsorbed*** in some physiologic states
- Dependent on muscle mass; i.e. poor marker for infants & elderly
- Cost: $1-$2

Cr versus CysC versus Combined Eq for eGFR



Challenges to SCr based definitions in neonates

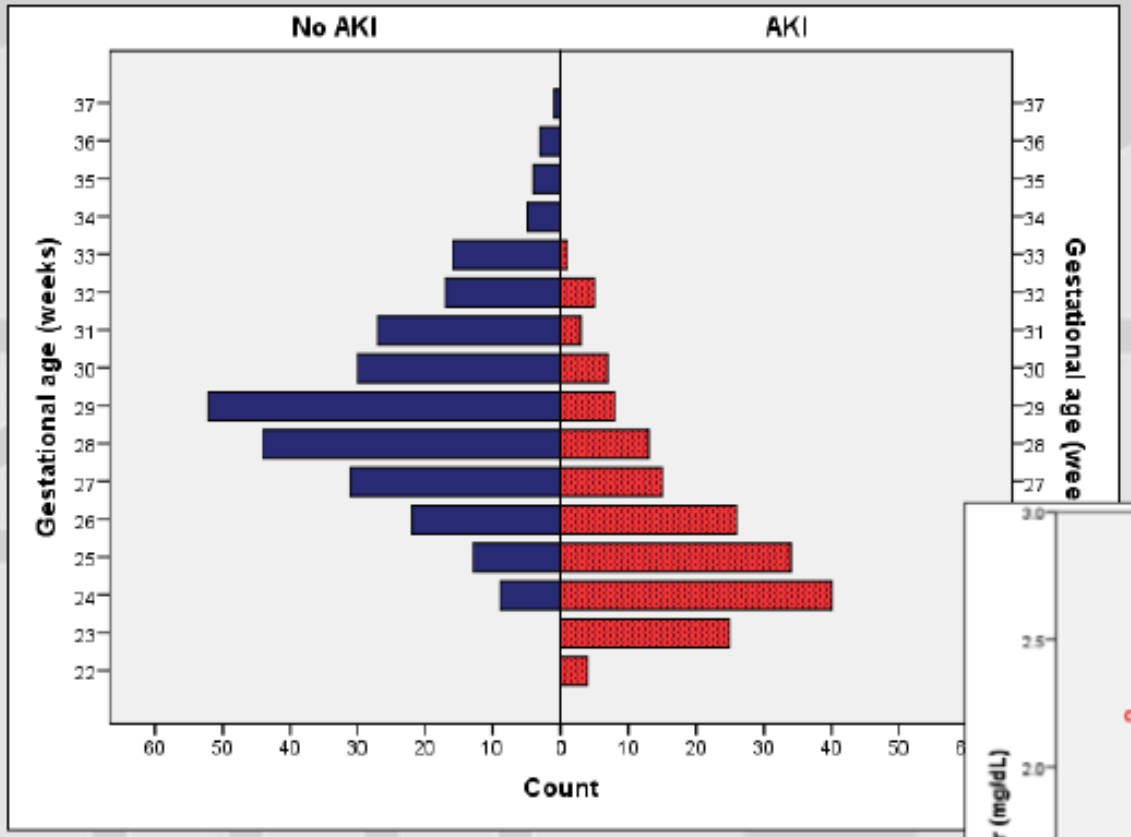
Normal Creatinine levels x gestational age



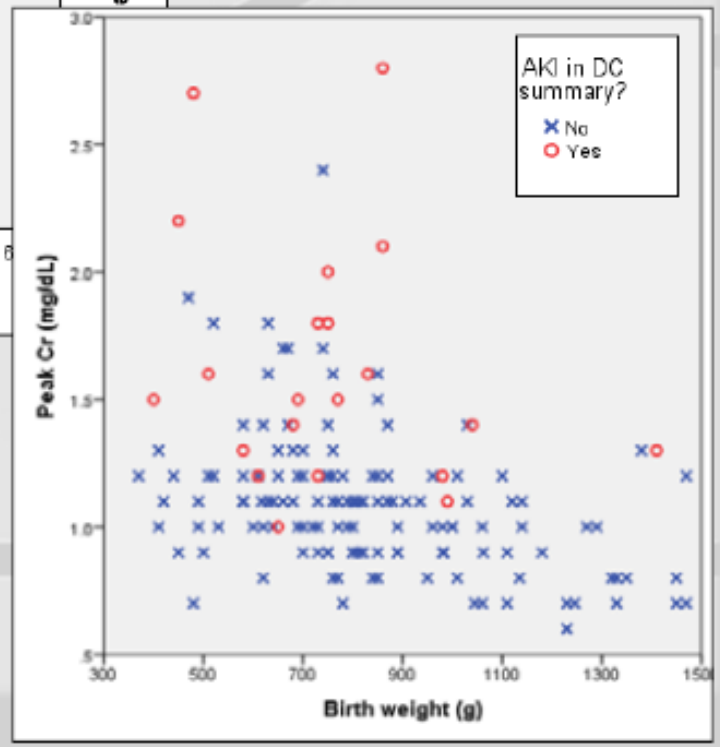
Gallini F: Pediatric Nephrology 2000 (15); 119-124

Underdiagnosis of Neonatal Acute Kidney Injury

- Serum creatinine is the only traditional marker of GFR
- “Myths” regarding serum creatinine in infants perpetuate under recognition of AKI
- Inulin as “gold standard” for measuring GFR is no longer available
- Cystatin C as a novel biomarker has only recently been accepted in adults & is not well studied in infants

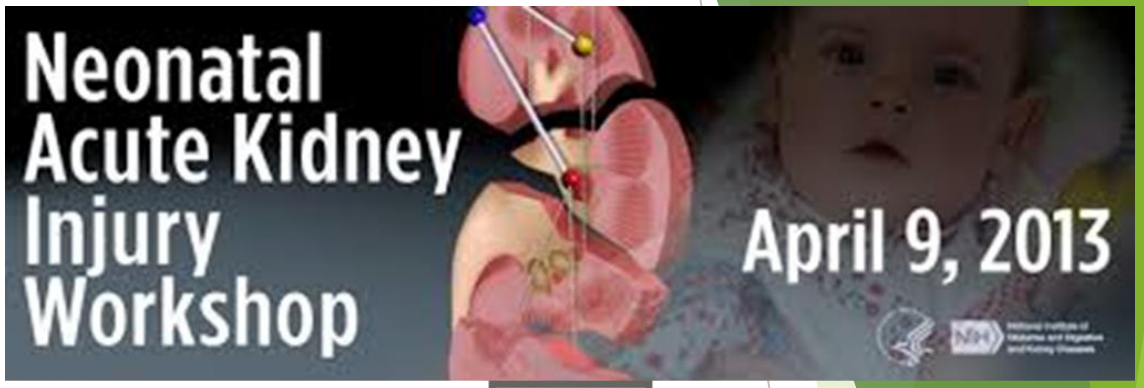


Seventy-five (16.5%) infants had multiple episodes of acute kidney injury.



Acute kidney injury was recorded in the discharge summary for only 13.5% of 155 acute kidney injury survivors.

Unique Challenges with Neonatal Kidney Failure



- Recognizing and defining the disease
- Collaboration with Neonatologists, Intensivists, Nephrologists, Nursing, the Institutions and **Industry**
- Adaptation and Innovation
- Education and propagation.

Neonatal KIDNEY Collaborative

Categorical AKI definitions

Urine output (common to all)	KDIGO stage[198,199] Serum creatinine		AKIN stage Serum creatinine		RIFLE class Serum creatinine or GFR	
<0.5 mL/kg/h for 6 h	Stage 1	Increase of 1.5–1.9 times baseline or ≥27 µmol/L (≥0.3 mg/dL) increase	Stage 1	Increase to >150–200% (1.5–2-fold) from baseline or ≥27 µmol/L (≥0.3 mg/dL) increase	Risk	Increase in serum creatinine ×1.5 or GFR decrease >25%
<0.5 mL/kg/h for 12 h	Stage 2	Increase of 2–2.9 times baseline	Stage 2	Increase to >200–300% (>2–3-fold) from baseline	Injury	Increase in serum creatinine ×2 or GFR decreased >50%
<0.3 mL/kg/h for 24 h or anuria for 12h	Stage 3	Increase of >3 times baseline or increase in serum creatinine to ≥354 µmol/L (≥4 mg/dL) or initiation of RRT (2.5 mg/dl)	Stage 3	Increase to >300% (>3-fold) from baseline or ≥354 µmol/L (≥4 mg/dL) with an acute increase of >44 µmol/L (>0.5 mg/dL) or initiation of RRT (2.5 mg/dl)	Failure	Increase in serum creatinine ×3 or serum creatinine ≥354 µmol/L (>4 mg/dL) with an acute rise ≥44 µmol/L (>0.5 mg/dL) or GFR decreased >75%
					ESRD	ESRD >3 months

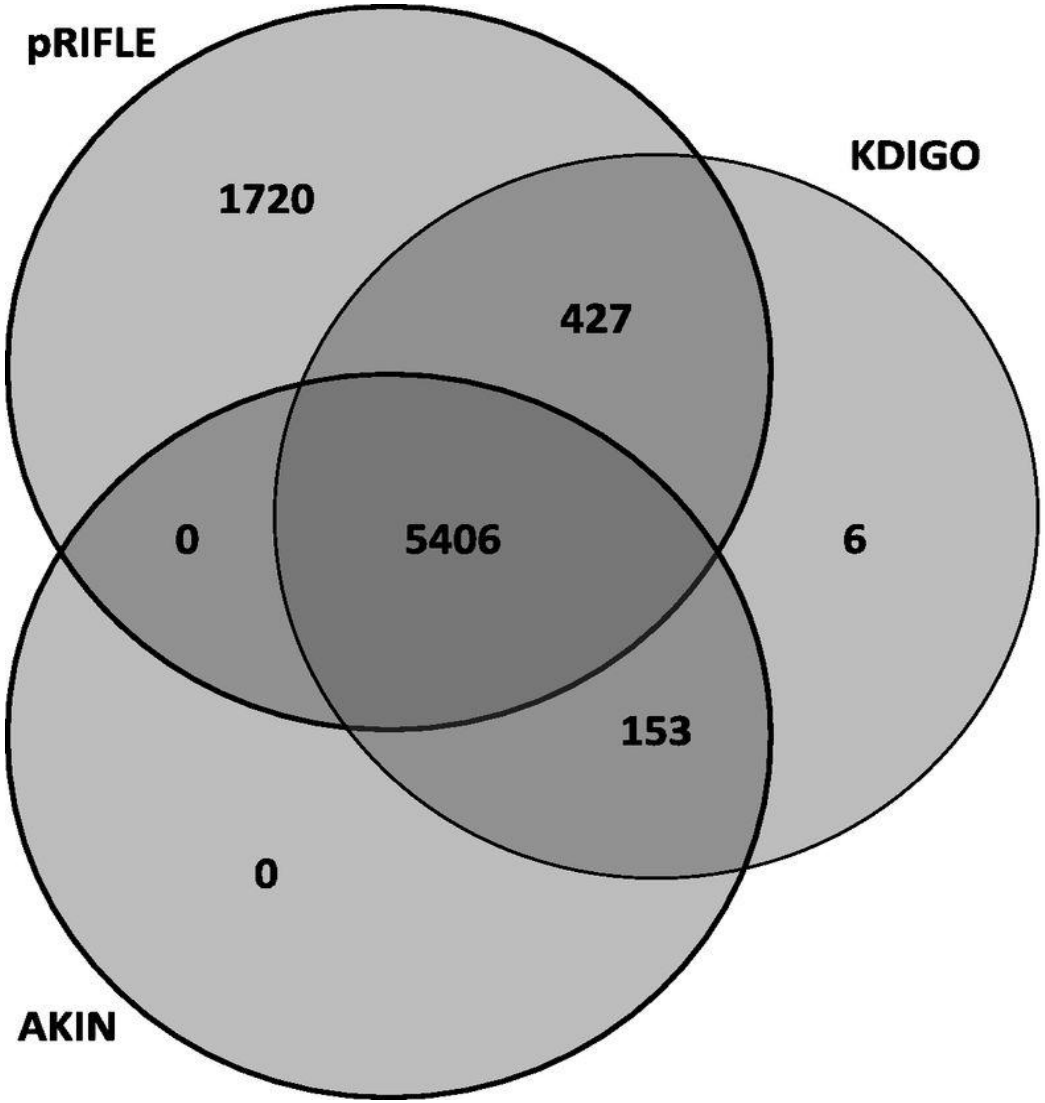
Reminder:

Creatinine is a functional marker

Interferences

Maternal influence

Definitional overlap and outcomes for specific patient cohorts.



	n	Mortality	LOS
AKI by all three	5406	2.7%	10 (5-21)
No AKI any	6146	0.8%	4 (2-6)
AKI pRIFLE only	1720	1.5%	5 (3-9)
AKI AKIN only	0	n/a	n/a
AKI KDIGO only	6	0%	6 (4-8)
Not diagnosed by pRIFLE	153	0%	5 (3-8)
Not diagnosed by AKIN	427	0.7%	12 (7-18)
Not diagnosed by KDIGO	0	n/a	n/a

Scott M. Sutherland et al. CJASN 2015;10:554-561

CJASN

Neonatal AKI KDIGO (Kidney Diseases: Improving Global outcomes) definition

Stage	Serum Creatinine	Urine output over 24 h
0	No change in serum creatinine or rise <0.3 mg/dl	>1 ml/kg/h
1 ***(Risk)***	SCr rise ≥ 0.3 mg/dl within 48 h or SCr rise ≥ 1.5 to 1.9 * reference SCr[a] within 7 days	>0.5 and ≤ 0.5ml/kg/h
2 ***(Injury)***	SCr rise ≥ 2 to 2.9 * reference SCr[a]	>0.3 and ≤0.5 ml/kg/h
3 ***(Failure)***	SCr rise ≥ 3* reference SCr[a] or SCr≥ 2.5 mg/dl* or Receipt of dialysis	≤0.3 ml/kg/h

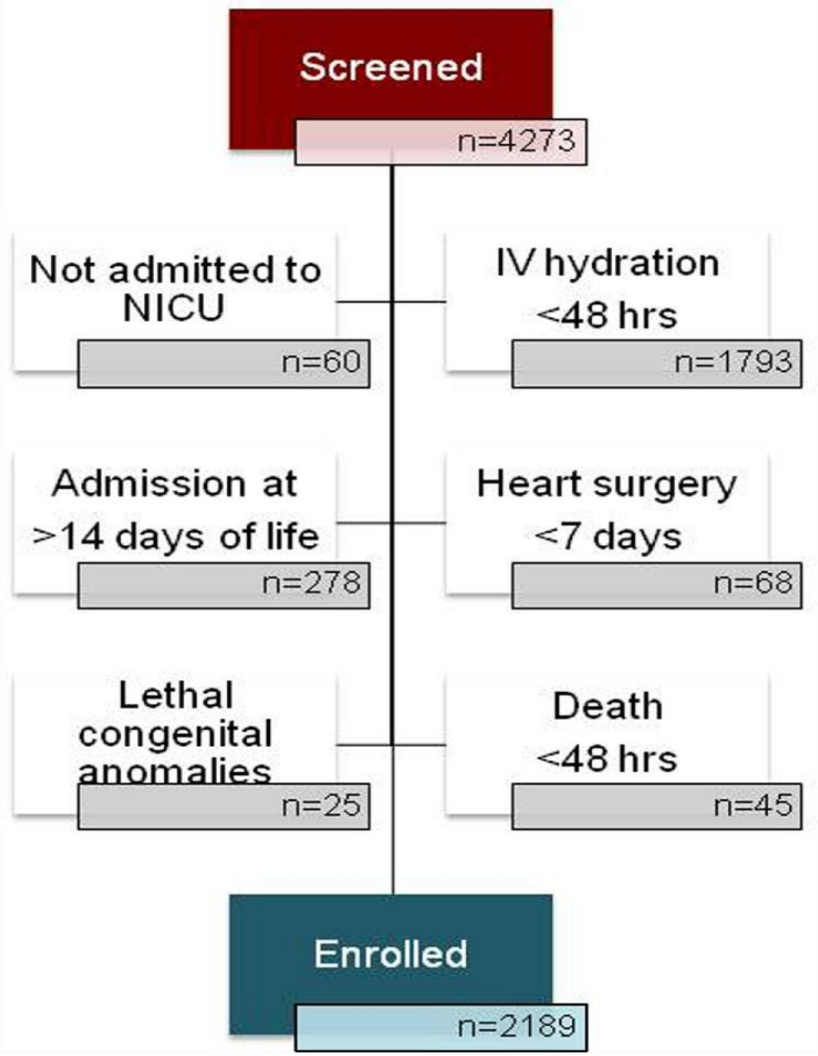
SCr: serum creatinine

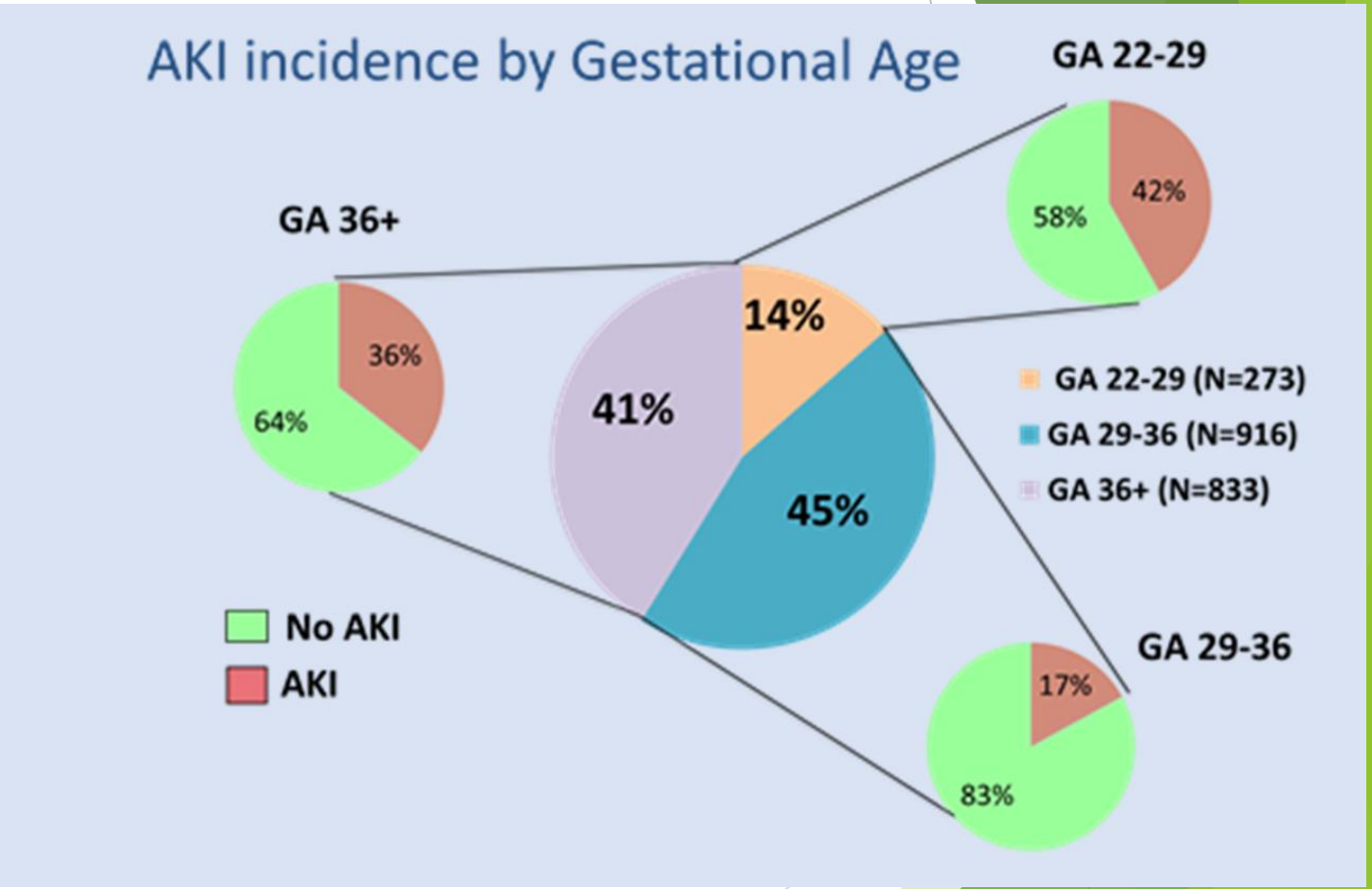
[a] Reference SCr is defined as the lowest previous SCr value

*SCr value of 2.5 mg/dL represents a clearance <10 ml/min/1.73m^2

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

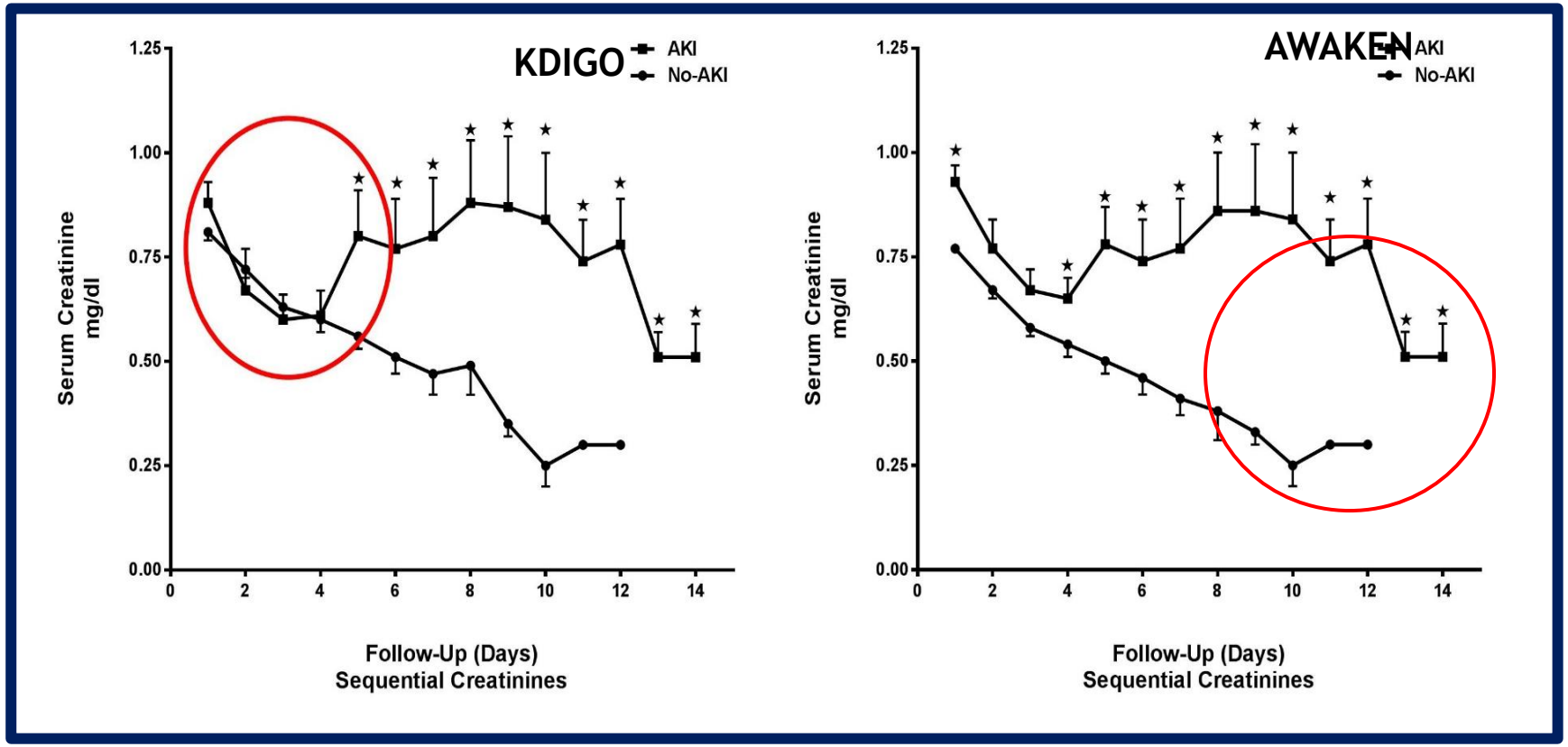
Lancet Child Adolesc Health 2017





Although the low gestational age group was the smallest number of the cohort, they had the highest incidence of AKI.

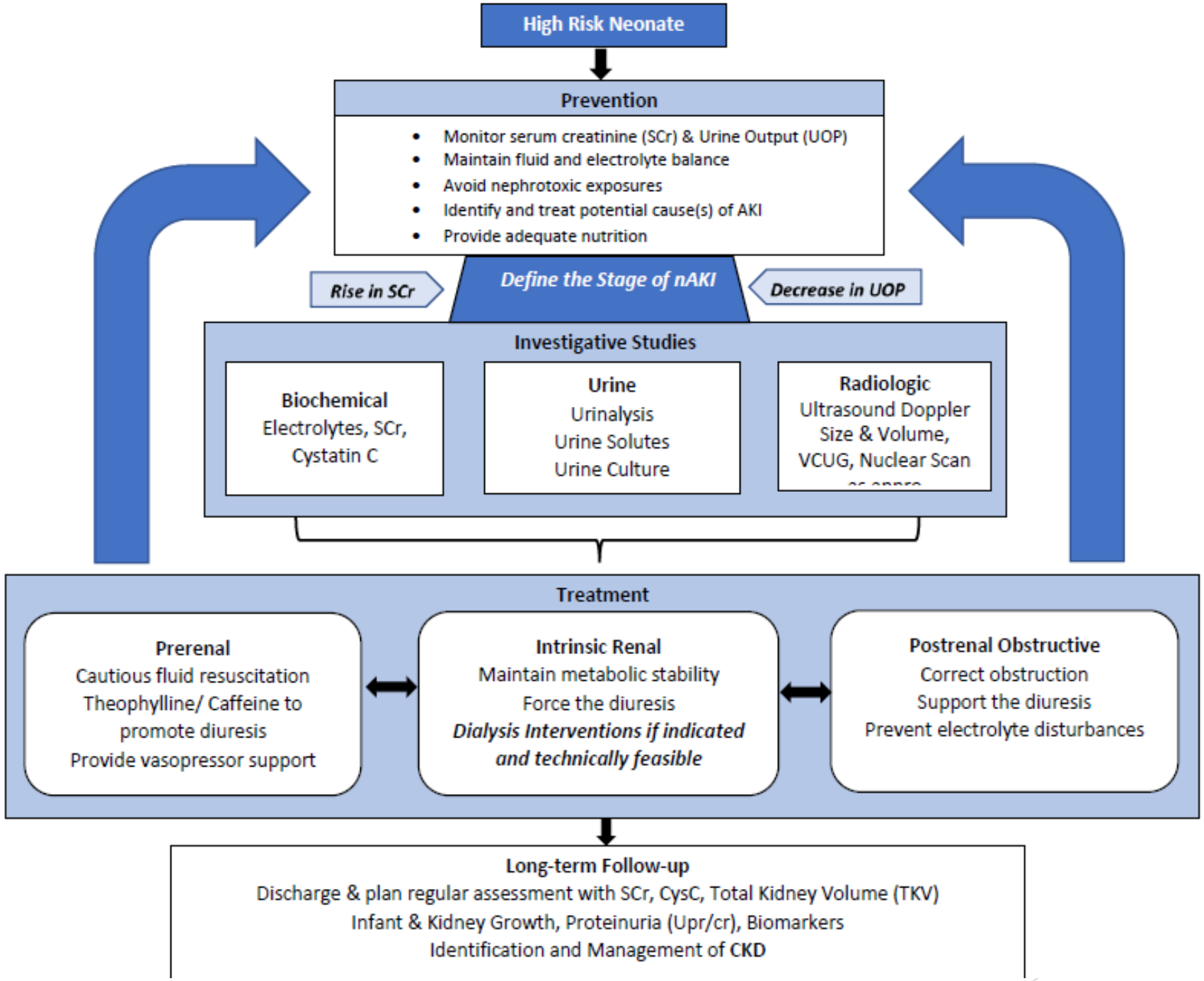
KDIGO vs AWAKEN: SCr Sequence



- 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.

Conclusions

- A diagnosis of Neonatal AKI by SCr-based definitions requires adjustment for gestational age and early developmental adaptations.
- Extremely preterm infants (<29 weeks' GA), have SCr values significantly above those infants of greater GA with an absolute SCr>1.5 mg/dL falling above the 95th percentile.
- The **m*aximum rise and lack of decline* in SCr** is likely the most reliable predictor of AKI when considering the KDIGO definition.
- Future refinements of SCr-based definitions, including provisions for GA, will be necessary in order to accurately diagnose Neonatal AKI.
- It is likely that other markers of **injury** rather than ***function*** are necessary to diagnose Neonatal AKI accurately.


High Risk Neonate
Prevention
Monitor serum creatinine (SCr) & Urine Output (UOP)
Maintain fluid and electrolyte balance
Avoid nephrotoxic exposures
Identify and treat potential cause(s) of AKI
Provide adequate nutrition
Rise in SCr
Define the Stage of nAKI
Decrease in UOP
Investigative Studies
Biochemical
Electrolytes, SCr,
Cystatin C
Urine
Urinalysis
Urine Solutes
Urine Culture
Radiologic
Ultrasound Doppler
Size & Volume,
VCUG, Nuclear Scan
Treatment
Prerenal
Cautious fluid resuscitation
Theophylline/ Caffeine to
promote diuresis
Provide vasopressor support
Intrinsic Renal
Maintain metabolic stability
Force the diuresis
Dialysis Interventions if indicated
and technically feasible
Postrenal Obstructive
Correct obstruction
Support the diuresis
Prevent electrolyte disturbances
Long-term Follow-up
Discharge & plan regular assessment with SCr, CysC, Total Kidney Volume (TKV)
Infant & Kidney Growth, Proteinuria (Upr/cr), Biomarkers
Identification and Management of CKD

Short definition of neonatal acute kidney injury

Short Definition Neonatal Acute Kidney Injury	
SCr Rise	Rise in SCr ≥0.3 mg/dL (27 mM/L)[a]
Peak SCr	Peak SCr ≥ 1.5 mg/dL (132 mM/L)[b]
Nadir SCr	Nadir SCr ≥ 0.5 mg/dL (44 mM/L)[c]

SCr: serum creatinine

[a] Reference SCr is defined as the lowest previous SCr value

[b] Peak SCr is the highest SCr from baseline

[c] Nadir SCr is the lowest SCr at discharge or 30 days of age

Etiologies of Neonatal AKI

Prerenal (85%) *(Risk)*	Intrinsic (12%) *(Injury ⟷ Failure)*	Postrenal (Obstructive) (3%) *(Failure ⟷ Injury)*
Volume contraction - Decreased placental perfusion - Increased insensible water losses - Increased Gastrointestinal losses	**Acute tubular Necrosis** - Drug induced - Hypoxia - Contrast nephropathy - Prolonged hypo-perfusion	**CAKUT (often with dysplasia)**
Hemorrhage - Feto-maternal hemorrhage - Twin-twin transfusion - Disseminated intravascular coagulation - Induced coagulopathy	**Drugs** - Aminoglycosides - Vancomycin - Angiotensin converting enzyme inhibitors - Acyclovir - Intravenous Immunoglobulin - Albumin	**Obstructive uropathy** - Posterior urethral valves - Urethral stenosis/ atresia - Ureteral pelvic or vesical junction abnormalities - Ureterocele(s) - Urogenital sinus anamoly - Calculi
Hypoxia Ischemia	**Vascular** - Renal Venous Thrombosis - Renal Artery thrombosis	**Fungal balls**
Sepsis		**Urate nephropathy**
Cardiac conditions: - History of patent ductus arteriosus - Asphyxia related cardiomyopathy - **Obstructive cardiac lesions (hypoplastic left heart, coarctation of the aorta)**	**Cystic renal diseases** - Multicystic dysplastic kidney - Polycystic kidney disease	
Polycythemia		

Urinary Indices in Pre-renal and Intrinsic nAKI

Parameter	Prerenal AKI	Intrinsic AKI
Urine Specific Gravity	>1.020	<1.010
Urine Osmolality (mOsm/L)	> 400	< 300
Urine/Plasma Osmolality Ratio	>1.3	<1.0
Urinary Na (mEq/L)	<10-50	30-90
FeNa (%)	<1%	>3%
Renal Failure Index	<3.0	>3.0
FeUN (%)	<35%	>50%
Urine Pr/Cr (mg/mg)	<0.3	>0.6
Urine Alb/Cr (mcg/mg)	<100	>100

Tenants of Conservative Management

- ***Restore fluid and electrolyte balance***
- Correct hyponatremia ***slowly*** avoiding hypertonic saline.
- Correct hypernatremia ***slowly*** and with enteral free water if possible.
- Correct hyperkalemia (>7.0 mM/L) *expeditiously but cautiously; then, prevent recurrence.*
  - Albuterol (beta-adrenergic agonists) by inhalation (0.4 mg in 2 ml of saline)
  - Glucose and insulin (Dextrose 10% at 5 ml/kg with regular insulin 0.1 units/kg) over 30 minutes.
  - ***Force a diuresis with theophylline (3-5 mg/kg) and furosemide (1-2 mg/kg)***
  - Discontinue all potassium containing intravenous/ enteral sources
  - Correct acidosis slowly with isotonic sodium bicarbonate solution (do not exceed 2% solution)
  - Sodium polystyrene sulfonate (SPS) (Kayexalate) preferably by pretreating the formula and avoid giving directly to the infant.
- Avoid nephrotoxic medications

Preventive and Pre-emptive therapies

- Vasoactive support
  - Dopamine & dobutamine
- Fluid Management
  - Recognition of capillary leak
  - Avoidance of excessive colloid
  - Recognize Critical Edema (10%=Increased Mortality)
- Avoidance of Nephrotoxic Drugs
- Diuretics
- Methylxanthines
  - Aminophylline
  - Caffeine

Unique Challenges with Neonatal AKI

PATIENT

- Small size
- Gestational Age
  - Active nephrogenesis
  - Developmental immaturity
- Recognition
- Underlying Cause(s) and severity of renal failure
- Control of Fluid/ volume status
- Co-morbidities with multi-organ failure

RESOURCES

- Available equipment
- Protective & supportive environment
- Experienced and skilled physician & nursing staff, Intinsivists, surgeons
- Ethical sensitivity and compassion for recognizing futility.

Indications for Renal Replacement Therapy

- 15 percent or greater fluid overload
- Oliguria not responsive to diuretics
- Escalating ventilatory requirements, especially if related to volume status (prior to intubation is preferred when possible)
- Need for adequate nutrition, especially when nutrition is compromised by fluid restriction or electrolyte abnormalities
- Need for provision of large volumes of medications or blood products in a patient already >10 percent fluid overloaded
- BUN between 80 and 100 mg/dL
- Life-threatening metabolic derangements (eg, hyperkalemia or hyperammonemia) that are refractory to medical management

Dialysis modalities for infants & small children

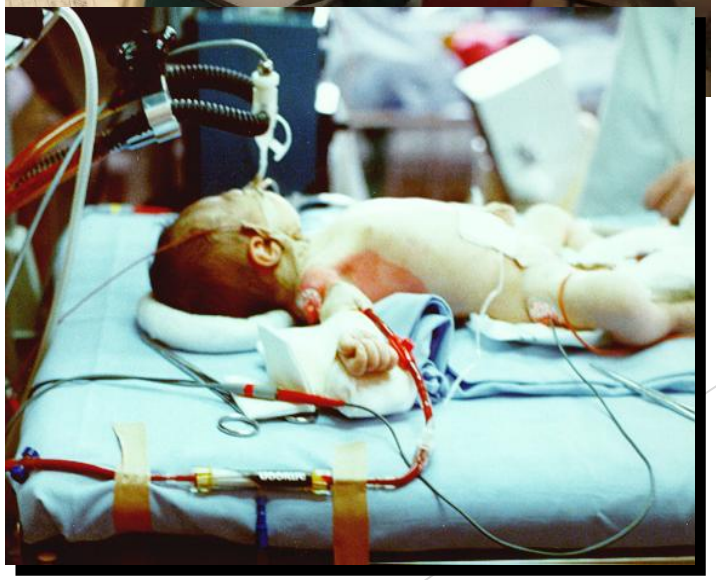
Modality	Efficiency	Fluid Removal	Extracorporeal Volume (mls)	Availability
Peritoneal Dialysis				
• Manual	+/-	+/-	0	Often
• Continuous Cycling Peritoneal Dialysis	+/-	+/-	0	Often
• Continuous Flow Peritoneal Dialysis	+/-	+/-	0	Rarely
Intermittent Hemodialysis	+	+	120-150	Often
Continuous Renal Replacement Therapy	+	+		
○ PRISMAFLEX™				
▪ HF1000	+	+	175	Often
▪ M60 *	+	+	125	Often
▪ HF20	+	+	45	Europe
○ Aquadex™ adapted	+/-	+	35	Rarely
○ Carpediem™ (Cardiac And Renal Pediatric Dialysis Emergency)	+	+	10	Europe
○ NIDUS™ (Newcastle Infant Dialysis Ultrafiltration System)	+	+	6.5	United Kingdom

*AN69 membrane causes bradykinin-release syndrome

Infants are ***NOT*** Small Children

- Blood Primes
- Access
- Machines are **Really** not designed for small children
  - Need high blood flow /kg
  - Need high clearances for citrate clearance
- Thermic Control is critical
- Not FDA approved for small children

Adapting Adult Machines to Infants and Small Children



- **Vascular access required**
- **Blood flow rates limited**
- **Blood prime**
- **AN69 Membrane with “Bradykinin release”**

Smaller circuits for smaller patients: improving renal support therapy with Aquadex™

David Askenazi[1] · Daryl Ingram[2] · Suzanne White[2] · Monica Cramer[1] · Santiago Borasino[3] · Carl Coghill[4] · Lynn Dill[1,2] · Frank Tenney[1] · Dan Feig[1] · Sahar Fathallah-Shaykh[1]

Pediatr Nephrol (2016) 31:853–860

- NO blood prime (ECV<35 ml)
- Small caliber vascular access
- Low blood flow rates
- SCUF + CVVH
- Available in the USA
- Relatively inexpensive

Continuous renal replacement therapy in neonates and small infants: development and first-in-human use of a miniaturised machine (CARPEDIEM)

Claudio Ronco, Francesco Garzotto, Alessandra Brendolan, Monica Zanella, Massimo Bellettato, Stefania Vedovato, Fabio Chiarenza, Zaccaria Ricci, Stuart L Goldstein

Lancet 2014; 383: 1807–13

- Developed for use for infants and small children.
- ECV 25 to 45 ml with different size filters
- Provides convection and diffusion
- Not available ion the USA

PLOS ONE

RESEARCH ARTICLE

Treatment of AKI in developing and developed countries: An international survey of pediatric dialysis modalities

Rupesh Raina[1,2]*, Abigail M. Chauvin[3], Timothy Bunchman[4], David Askenazi[5], Akash Deep[6], Michael J. Ensley[7], Vinod Krishnappa[2], Sidharth Kumar Sethi[8]

	Developing Countries	Developed Countries	p
Availability of pediatric nephrologist	35.4% (17/48)	100% (175/175)	0.000
Availability of dedicated pediatric dialysis unit	33.3% (16/48)	91% (159/175)	0.000
Institute's dialysis modality of choice in infants			
PD	68.5% (33/48)	5.7% (10/175)	0.000
HD	12.5% (6/48)	72% (126/175)	0.000
CRRT	10.4% (5/48)	24% (42/175)	0.041
SLED	8.3% (4/48)	1.1% (2/175)	0.006

Survey of Worldwide Pediatric Nephrologists Re: RRT

	Developing Countries	Developed Countries	p
Indication for CRRT			
Fluid overload in critically ill child	12.5% (2/16)	40% (42/105)	0.033
Hyperkalemia	81.2% (13/16)	100% (105/105)	0.000
Persistent metabolic acidosis	31.2% (5/16)	61.9% (65/105)	0.021
Hyperammonemia secondary to inborn errors and liver failure	100% (16/16)	100% (105/105)	1
Prefered mode of CRRT			
CVVH	12.5% (2/16)	17.1% (18/105)	0.637
CVVHD	43.7% (7/16)	14.2% (15/105)	0.004
CVVHDF	12.5% (2/16)	31.4% (33/105)	0.120
Depends on the clinical situation	25% (4/16)	35.2% (37/105)	0.422

Key Points

- There is to date no validated definition of *neonatal acute kidney injury* (nAKI).
- Serum creatinine-based definitions of nAKI will vary with gestational and postnatal age.
- Early recognition and reversal of Stage 1 (Prerenal) AKI requires risk assessment and frequent monitoring of renal function and injury.
- Prevention should include avoidance of nephrotoxic exposures and early intervention for reversal of cause, i.e. relieve obstruction, treat sepsis and support blood pressure.
- Management should be directed at conservative fluid resuscitation, maintenance of diuresis, electrolyte balance and nutritional support.
- Dialytic interventions require specialized technical adaptations of treatment modalities and consideration of co-morbidities.
- Long-term follow-up is essential to recognize and treat chronic kidney disease, a likely sequela of nAKI.

IPNA

GREAT CARE FOR LITTLE KIDNEYS, EVERYWHERE

JAMAICA KIDNEY KIDS FOUNDATION