NEONATAL AKI: WHAT WE SHOULD KNOW

Prof. Ashraf M A Bakr

Prof. of pediatrics, Mansoura Faculty of Medicine,
Provost –Hertfordshire University
Consultant, Pediatric Nephrology, Mansoura University Children's Hospital

Agenda

- Is it easy to diagnose neonatal AKI
- Are neonates more vulnerable to develop AKI
- What are the risk factors for neonatal AKI
- How do we evaluate
- Could we prevent neonatal AKI
- How do we manage
- What are the sequelae

Definition & Classification

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Table 1. Synoptic view of adult, paediatric and neonatal RIFLE

	Creatinine criteria			Urine output criteria		
	RIFLE	*pRIFLE*	*nRIFLE*	*RIFLE*	*pRIFLE*	*nRIFLE*
Risk	Increased creatinine × 1.5 or GFR decreases >25%	eCCl decrease by 25%	?	UO ≤ 0.5 mL/kg/h × 6 h	UO < 0.5 mL/kg/h for 8 h	UO < 1.5 mL/kg/h for 24 h
Injury	Increased creatinine × 2 or GFR decreases >50%	eCCl decrease by 50%	?	UO ≤ 0.5 mL/kg/h × 12 h	UO < 0.5 mL/kg/h for 16 h	UO < 1.0 mL/kg/h for 24 h
Failure	Increased creatinine × 3 or GFR decreases >75% or creatinine ≥4 mg/dL (acute rise of ≥4 mg/dL)	eCCl decrease by 75% or eCCl <35 mL/min/1.73 m^2	?	UO ≤ 0.3 mL/kg/h × 24 h or anuria × 12 h	UO < 0.3 mL/kg/h for 24 h or anuric for 12 h	UO < 0.7 mL/kg/h for 24 h or anuric for 12 h
Loss	Persistent failure >4 weeks					
End stage	Persistent failure >3 months					

Question mark ('?') is intended to mean uncertain thresholds.
GFR, glomerular filtration rate; Ecl, estimated creatinine clearance; UO, urine output.

Definition & Classification

Table 1. Proposed neonatal AKI definition modifications from KDIGO pediatric AKI definition, using SCr and urine output criteria

Stage	Serum creatinine criteria (in mg/dl)			Urine output criteria (in ml/kg/h)[a]		
	Pediatric definition	Neonatal modification: 2012	Neonatal modification: 2015–2016	Pediatric definition	Neonatal modification: 2013	Neonatal modification: 2016
1	≥0.3 Rise within 48 h or ≥1.5–1.9 × rise from baseline[b] within 7 days	≥0.3 rise or ≥1.5–1.9 × rise from baseline (defined as previous lowest/ trough value)	≥0.3 rise within 48 h or ≥1.5–1.9 × rise from baseline (previous lowest value) within 7 days	<0.5 for 8 hours	<1.5 for 24 h	≤1 for 24 h
2	≥2–2.9 × rise from baseline	Unchanged	Unchanged	<0.5 for ≥16 h	<1 for 24 h	≤0.5 for 24 h
3	≥3 × rise from baseline or ≥4.0 or eGFR <35 ml/min per 1.73 m^2 or RRT initiation	≥3 × rise from baseline or ≥2.5 or RRT initiation	≥3 × rise from baseline or ≥2.5 or RRT initiation	<0.3 for ≥24 h or anuria for ≥12 h	<0.7 for 24 h or anuria for 12 h	≤0.3 for 24 h

AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; RRT, replacement therapy; SCr, serum creatinine concentration.

[a]The published KDIGO definition proposes timing cutoffs for low urine output to be >6 h for stage 1 (instead of >6 h) and >12 h for stage 2 (instead of >16 h). The pediatric literature to date has consistently utilized urine output decrease timing cutoffs as displayed in the table.

[b]Baseline SCr: no clear guideline on how to define pediatric baseline SCr. In the literature, baseline SCr has most commonly been defined as the lowest SCr measured in the previous 3 months.

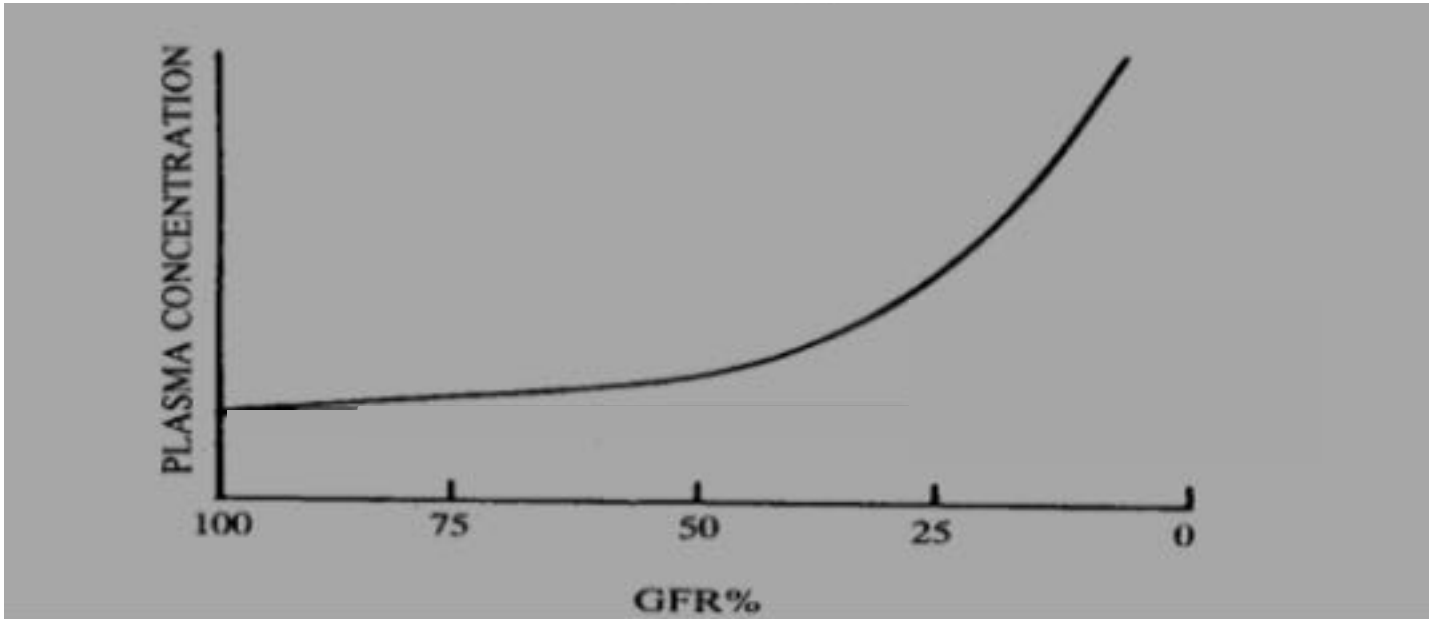
Definition & Classification

Stage	SCr	UOP
0	No change in SCr level or rise <0.3 mg/dL	≥0.5 mL/kg per h
1	Increase in SCr level of ≥0.3 mg/dL within 48 h or rise in SCr level ≥1.5–1.9 times the reference SCr level[a] within 7 d	<0.5 mL/kg per h for 6–12 h
2	Rise in SCr level ≥2–2.9 times the reference SCr level[a] within 7 d	<0.5 mL/kg per h for ≥12 h
3	SCr level ≥3 times the reference SCr level[a] or SCr level >2.5 mg/dL[b] or receipt of RRT	<0.3 mL/kg per h for ≥24 h or anuria for ≥12 h

Jetton et al; Front Pediatr. (2016)

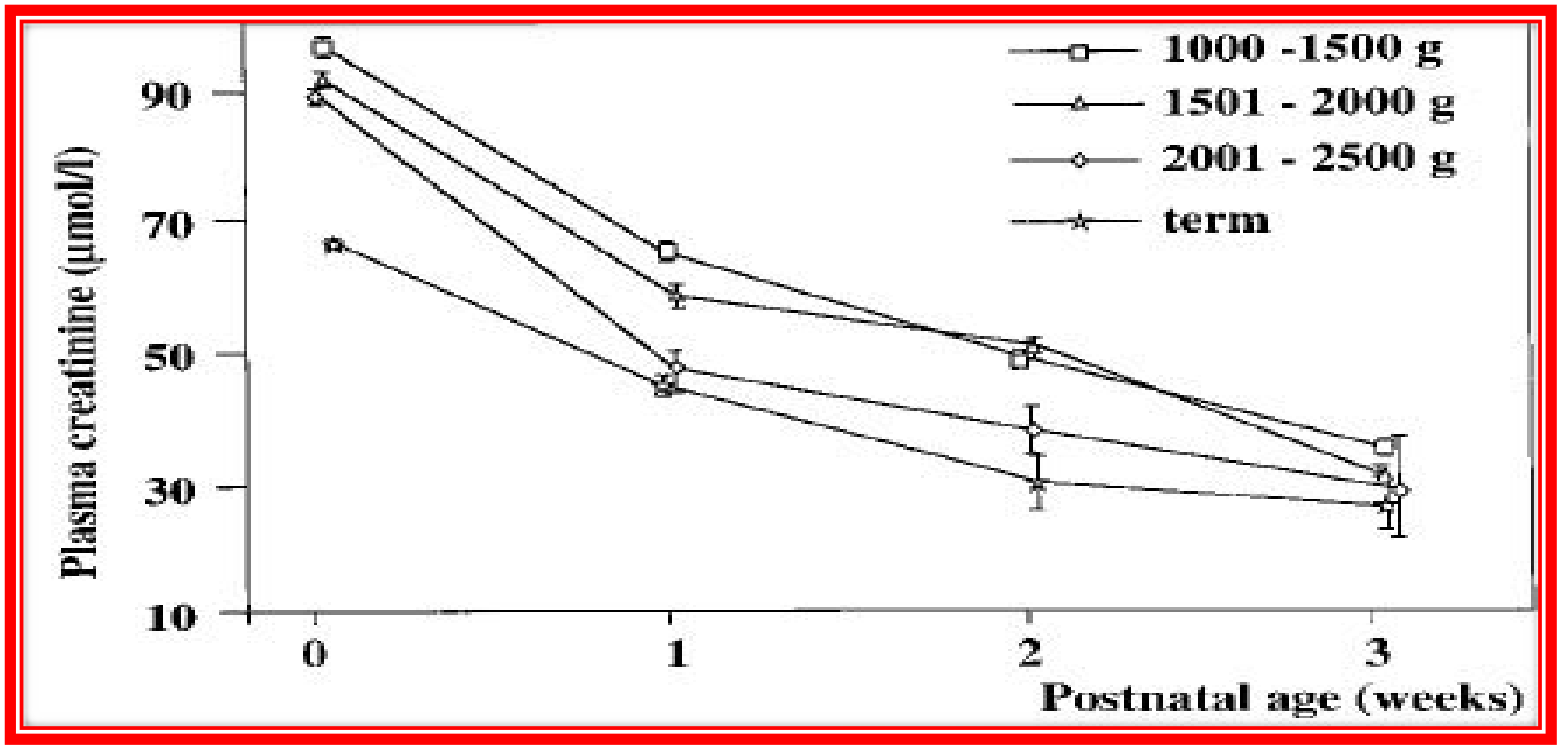
Limitations

Serum creatinine



Limitations

Serum creatinine



Bueva & Guignar; Pediatr Res., (1994)

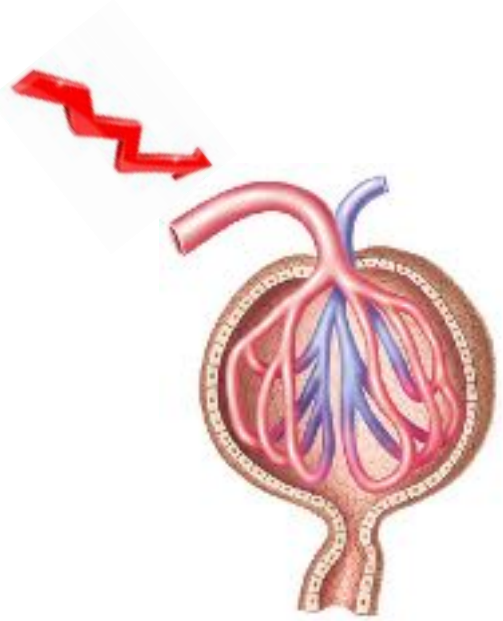
Limitations

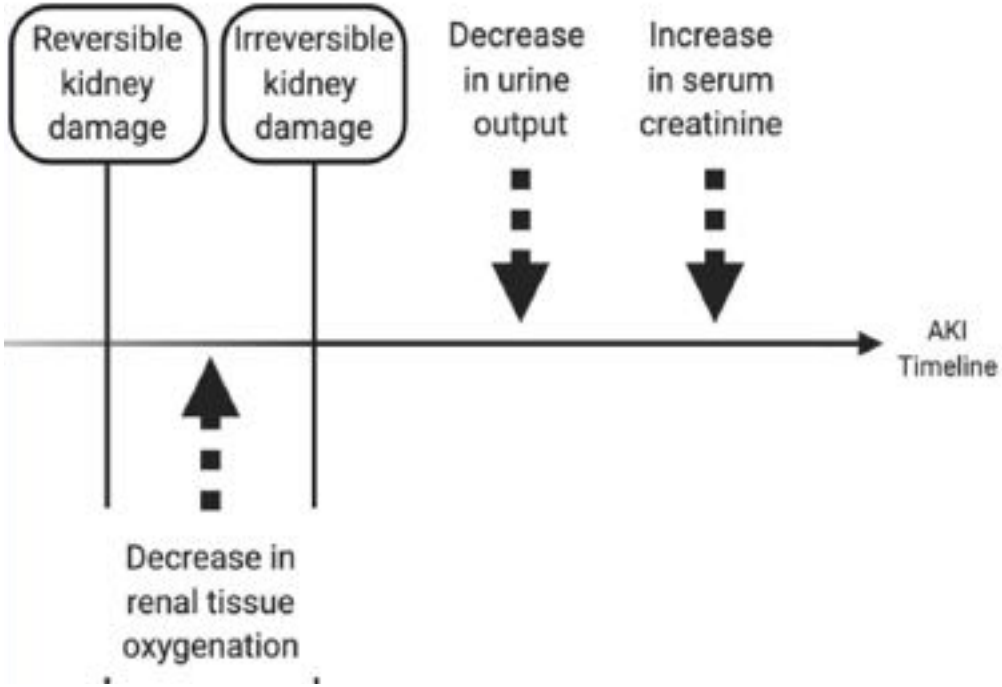
UOP

- Neonates often have ***non-oliguric*** AKI due to their tubular immaturity.
- ***Low accuracy*** of urine collection in a neonate due to lower rates of urinary catheter placement and reliance on diaper weights.

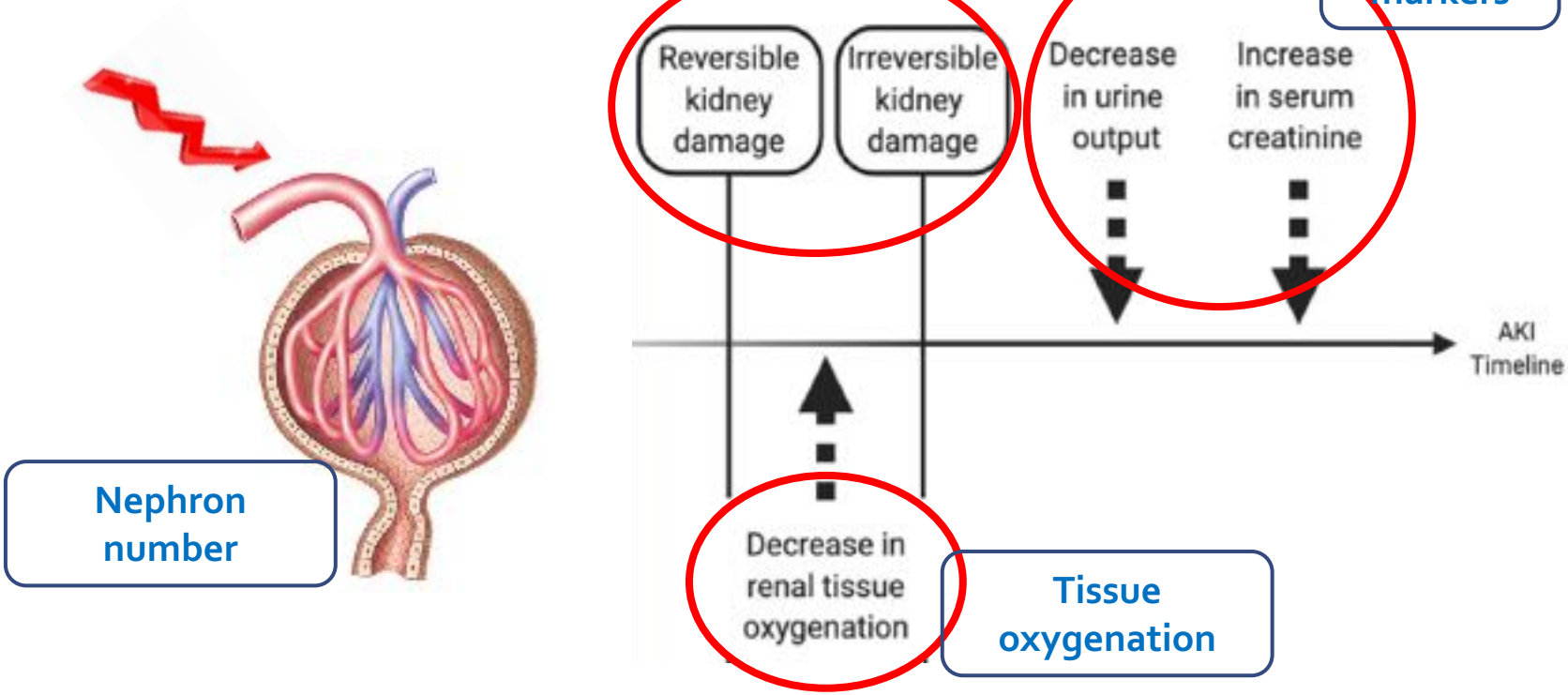
Goldstein; Front Pediatr. (2019)

Timeline of changes in a patient with AKI





New markers of AKI



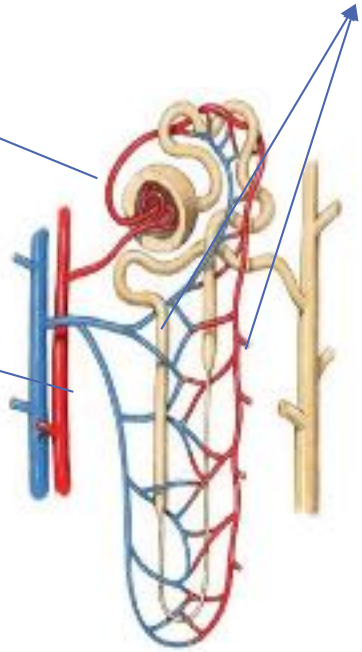
New markers of AKI

Markers of glomerular function:

- Cystatin C
- NGAL
- RBP
- Hepcidin

Markers of tubular function:

- Cystatin C
- NGAL
- RBP



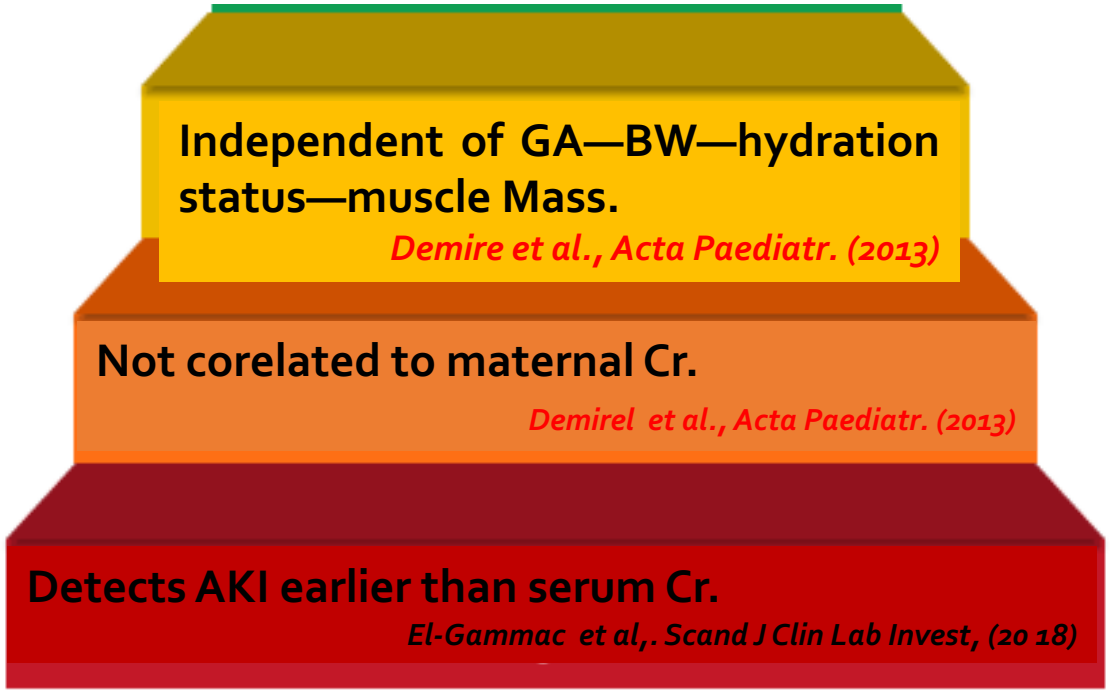
Markers of tubular damage:

- NAG
- α-GST
- Π-GST
- γ-GT
- NAGL ⟶ DCT
- KIM-1 ⟶ PCT
- RBP
- L-FABP
- α-/β2 macroglobulin
- IGFBP-7 } G1 cycle arrest
- TIMP-2 } G1 cycle arrest
- microRNA
- Netrin-1
- UMOD ⟶ LH

Recognition

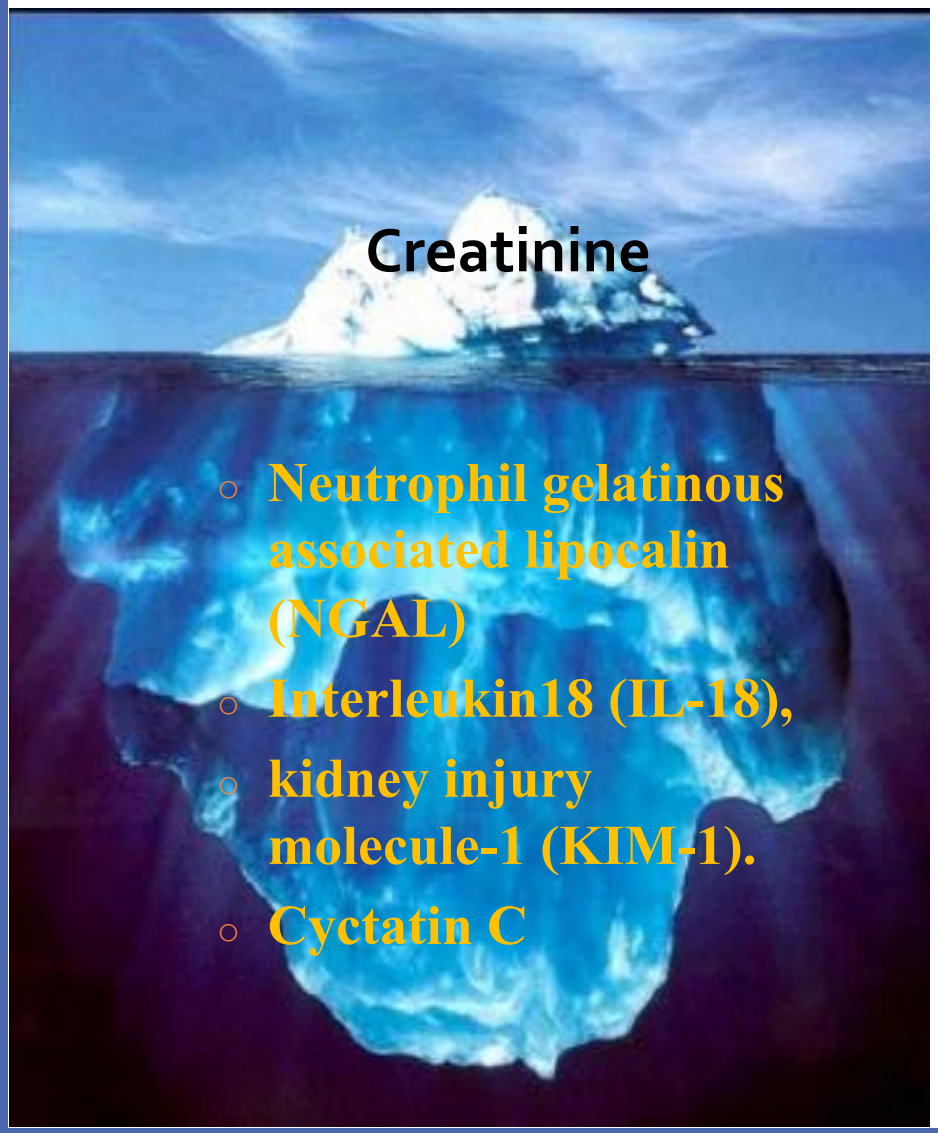
New biomarkers

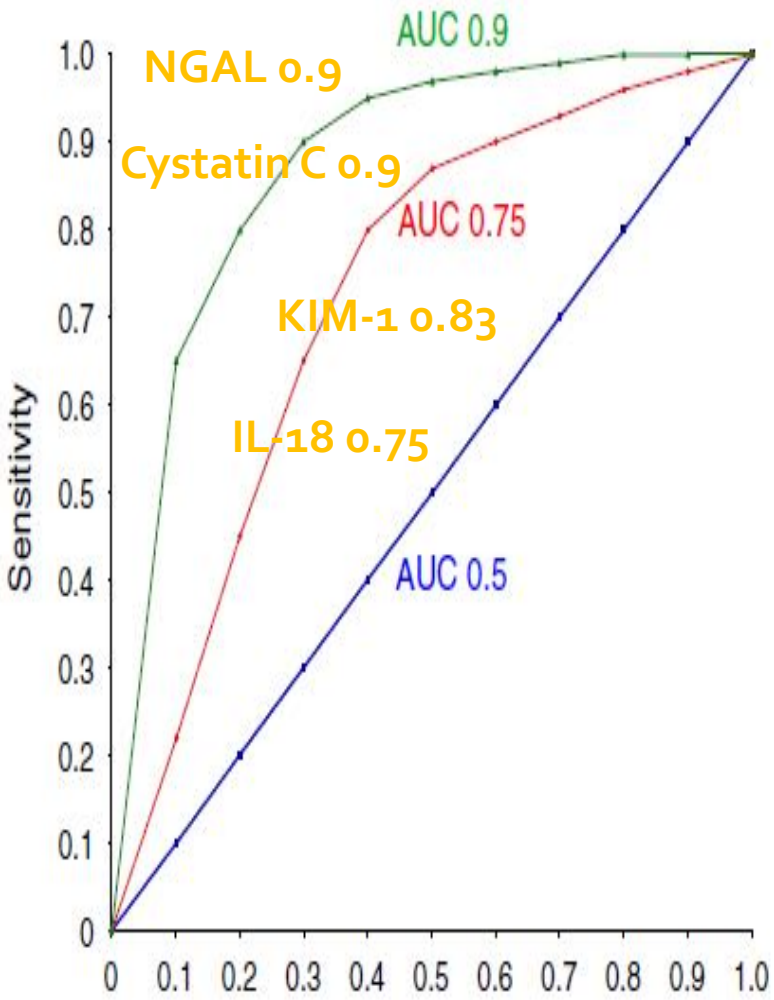
Cystatin-C



Advantages

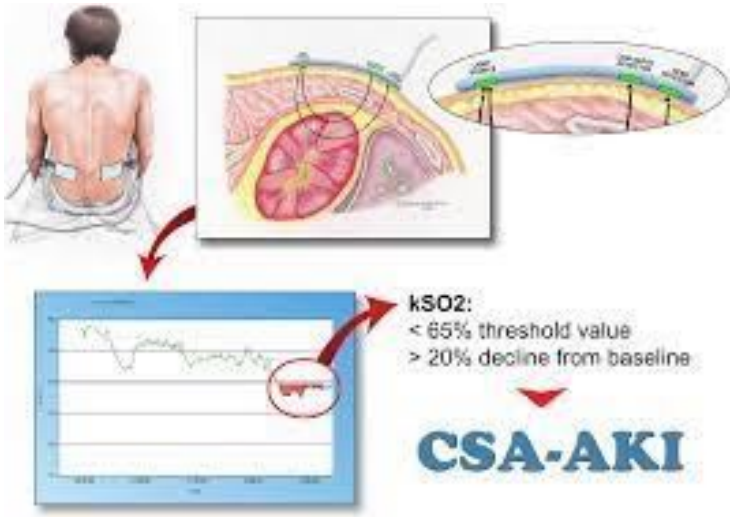
New biomarkers





Tissue oxygenation

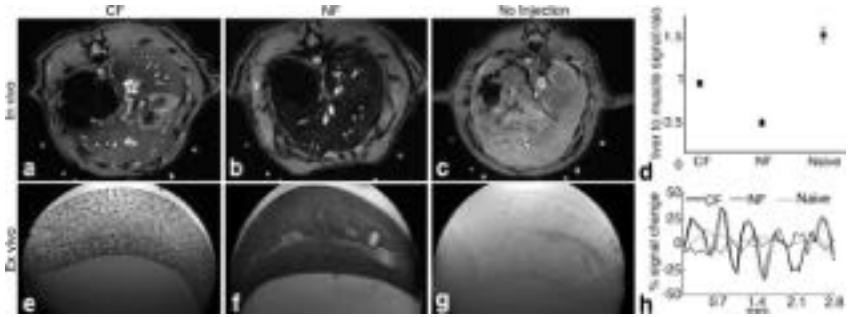
Renal tissue oxygenation *(RrSO2)* monitoring by using Near-infrared spectroscopy *(NIRS)* is a surrogate for local tissue oxygen use.



Harer et al,. Front Pediatr. (2020)

Nephron number

- The ***radial glomerular count*** **by using** ***Cationic ferritin-enhanced MRI*** **is a surrogate marker of glomerulogenesis.**



Charlto; pediatr Res (2020).

Definition & Classification

Neonatal modified KDIGO definition is still used as the STANDARD definition for neonatal AKI.

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

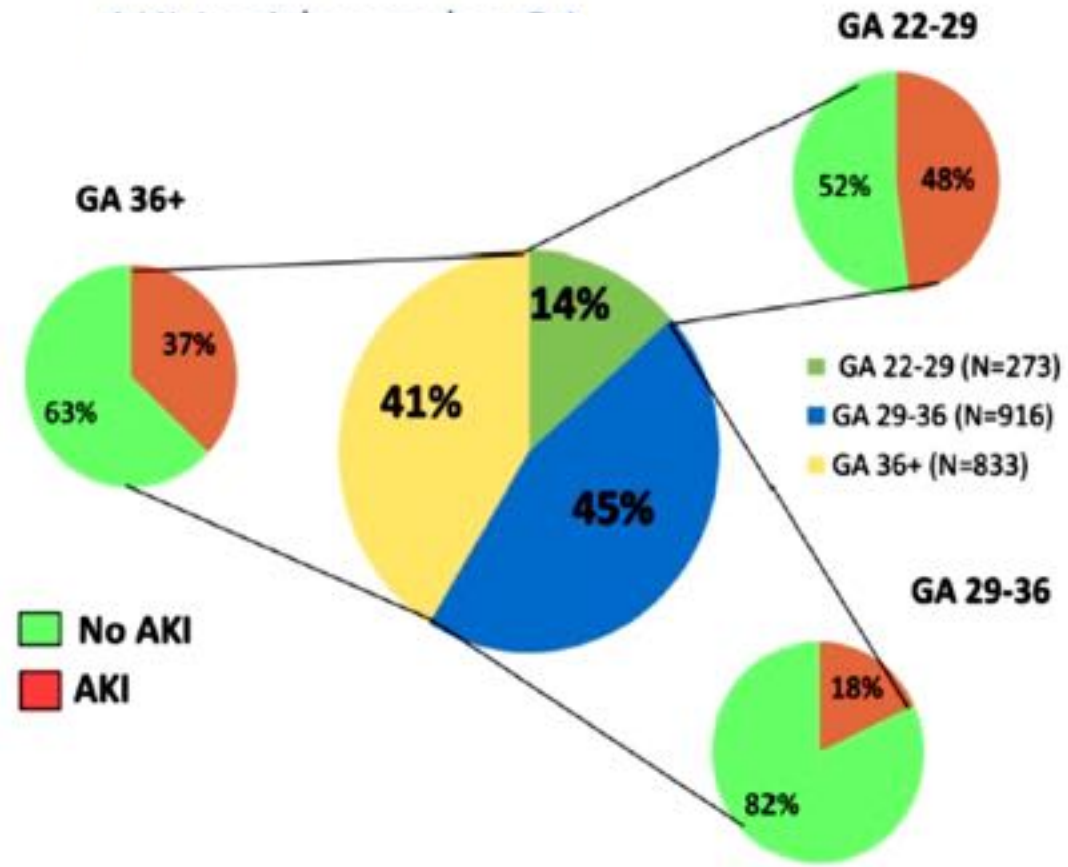
Jennifer G. Jetton, MD[1], Louis J. Boohaker, MPH[2], Sidharth K. Sethi, MD[3], Sanjay Wazir, MD[4], Smriti Rohatgi, MD[5], Danielle E. Soranno, MD[6], Aftab S. Chishti, MD[7], Robert Woroniecki, MD[8], Cherry Mammen, MD[9], Jonathan R. Swanson, MD[10], Shanty Sridhar, MD[11], Craig S. Wong, MD[12], Juan C. Kupferman, MD[13], Russell L. Griffin, PhD[14], and David J. Askenazi, MD[15,*] on behalf of the Neonatal Kidney Collaborative (NKC)[**]

Methods—All neonates admitted to 24 participating neonatal intensive care units from four countries (Australia, Canada, India, United States) between January 1 and March 31, 2014, were screened. Of 4273 neonates screened, 2022 (47·3%) met study criteria. Exclusion criteria included: no intravenous fluids ≥48 hours, admission ≥14 days of life, congenital heart disease requiring surgical repair at <7 days of life, lethal chromosomal anomaly, death within 48 hours, inability to determine AKI status or severe congenital kidney abnormalities. AKI was defined using a standardized definition —i.e., serum creatinine rise of ≥0.3 mg/dL (26.5 mcmol/L) or ≥50% from previous lowest value, and/or if urine output was <1 mL/kg/h on postnatal days 2 to 7.

Lancet Child Adolesc health (2018)

AKI Incidence by GA

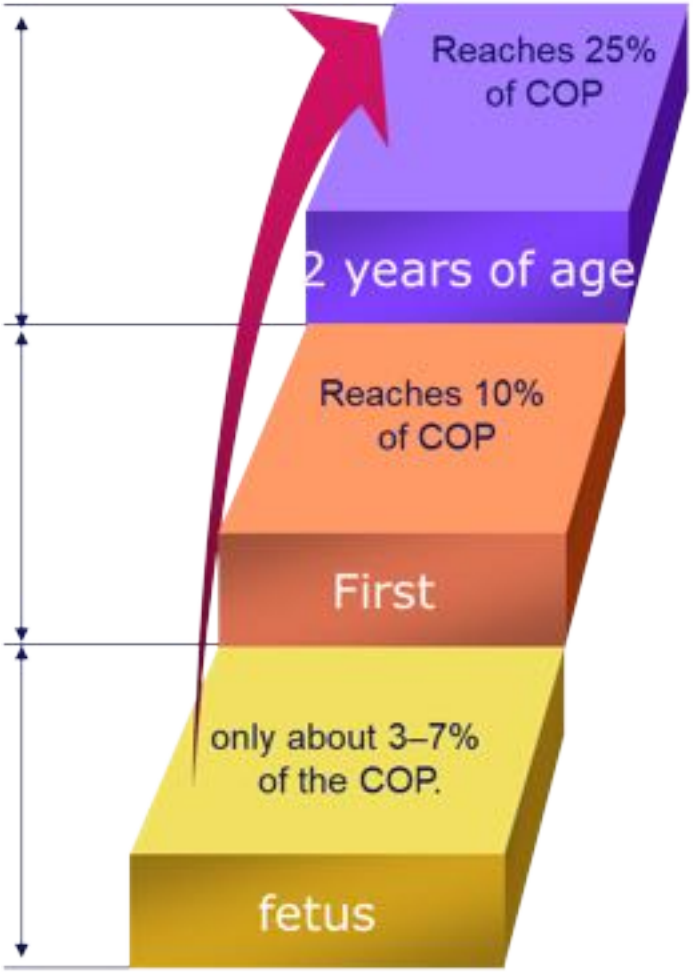
29.5%



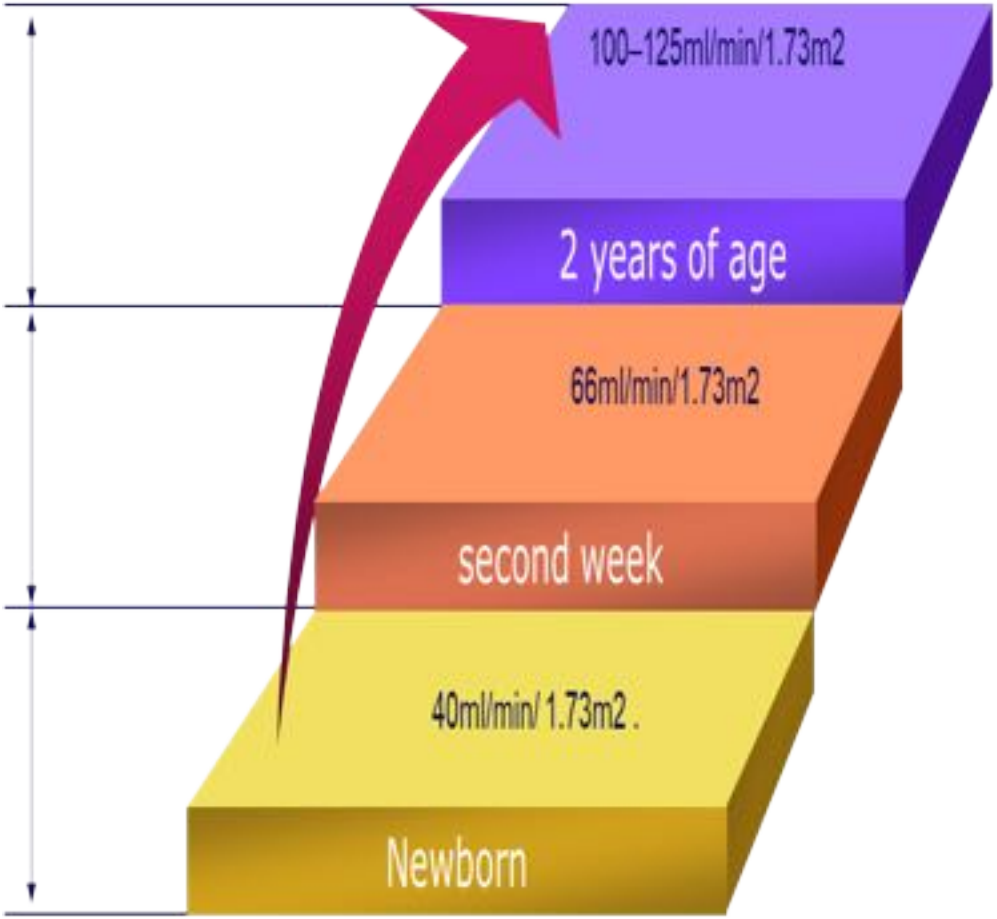
Schematic representation of gestational age distribution in the cohort Gestational age (GA) is presented in weeks. AKI, acute kidney injury.

Vulnerability

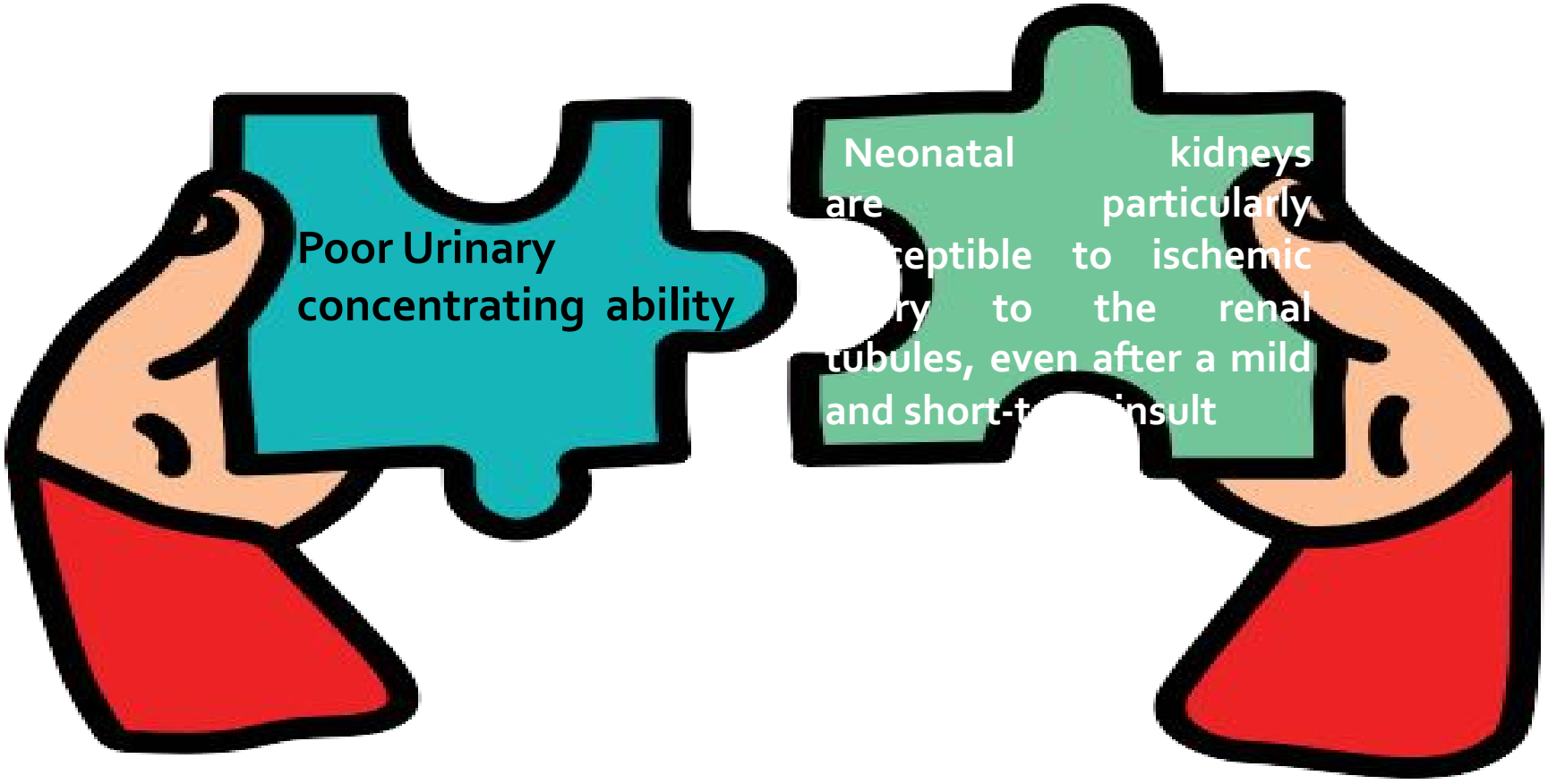
RBF



GFR



Vulnerability



Vulnerability

Physiological immaturity in newborns let them more vulnerable to AKI.

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- What are the sequelae

Inclusion Criteria

CLINICAL RESEARCH ARTICLE

Neonatal acute kidney injury risk stratification score: STARZ study

Sanjay Wazir[1], Sidharth Kumar Sethi[2], Gopal Agarwal[1], Abhishek Tibrewal[3], Rohan Dhir[2], Naveen Bajaj[4], Naveen Parkash Gupta[5], Shishir Mirgunde[6], Jagdish Sahoo[7], Binesh Balachandran[8], Kamran Afzal[9], Anubha Shrivastava[10], Jyoti Bagla[11], Sushma Krishnegowda[12], Ananth Konapur[13], Kritika Soni[2], Abhyuday Rana[14], Timothy Bunchman[15] and Rupesh Raina[3]

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BACKGROUND: Neonates admitted in the neonatal intensive care unit are vulnerable to acute kidney injury leading to worse outcomes. It is important to identify "at-risk" neonates for early preventive measures.

METHODS: The study was a multicenter, national, prospective cohort study done **11 centers in India** multivariable logistic regression technique with step-wise backward elimination method was used, and a "Risk Prediction Scoring" was devised [the STARZ score].

RESULTS: The neonates with admission in the NICU within <25.5 h of birth, requirement of positive pressure ventilation in the delivery room, <28 weeks gestational age, sepsis, significant cardiac disease, urine output <1.32 ml/kg/h or serum creatinine ≥0.98 mg/dl during the first 12 h post admission, use of nephrotoxic drugs, use of furosemide, or use of inotrope had a significantly higher risk of AKI at 7 days post admission in the multivariate logistic regression model. This scoring model had a sensitivity of 92.8%, specificity of 87.4% positive predictive value of 80.5%, negative predictive value of 95.6%, and accuracy of 89.4%.

CONCLUSIONS: The STARZ neonatal score serves to rapidly and quantitatively determine the risk of AKI in neonates admitted to the neonatal intensive care unit.

Pediatric Research (2022) 91:1141–1148; https://doi.org/10.1038/s41390-021-01573-9

Risk Factors

Table 1. The significant variables in the best fit model identified based on multivariate logistic regression technique with stepwise backward elimination method [$n = 310$; 31 independent variables].

Variables	β coefficient	Adjusted RR (95% CI)	p value
Age at entry in NICU[a] (<25.5; Ref.: ≥25.5 h)	1.29	2.06 (1.05–2.97)	0.04
PPV in the delivery room (Yes; Ref.: No)	1.66	1.91 (1.05–2.32)	0.04
Gestational age (<28; Ref.: ≥28 weeks)	1.51	2.01 (1.02–2.74)	0.02
Sepsis (during the NICU stay) (Yes; Ref.: No)	1.46	1.98 (1.04–2.54)	0.04
Significant cardiac disease (Yes; Ref.: No)	2.16	2.81 (1.06–3.56)	0.04
Urine output[a,b] (<1.32; Ref.: ≥1.32 ml/kg/h)	1.59	2.29 (1.21–3.01)	0.01
Serum creatinine[a,b] (≥0.98; Ref.: <0.98 mg/dl)	4.60	13.44 (8.44–15)	<0.001
Use of nephrotoxic drugs (Yes; Ref.: No)	2.46	2.76 (1.6–3.19)	0.004
Use of furosemide (Yes; Ref.: No)	1.96	2.39 (1.06–2.98)	0.04
Use of inotrope(s) (Yes; Ref.: No)	3.78	2.79 (1.01–2.91)	0.04

Nephrotoxic drugs included vancomycin or colistin or amphotericin B. Inotrope drugs included dopamine or dobutamine or epinephrine or norepinephrine. Adjusted for all the variables with $p < 0.05$ in the univariate analysis. Enteral fluid intake and serum urea were not considered in the multivariate analysis due to missing data in >50% of the patients.

PPV positive pressure ventilation, *Ref.* reference, *NICU* neonatal intensive care unit.

[a]The continuous variables observed to be independently associated with AKI in Mann–Whitney *U* test were categorized into two groups based on the cut-off threshold value (sensitivity and specificity is observed to be the highest) identified by ROC analysis.

[b]First 12 h post admission in NICU.

Risk Factors

Table 3. Score assigned to each significant variable of the best fit model.

Variables	β coefficient	β coefficient × 10	Score to the nearest integer/100	Assigned score
Age at entry in NICU[a] (h)				
<25.5	1.29	12.9	6	6
≥25.5				0
PPV in the delivery room				
Yes	1.66	16.6	7	7
No				0
Gestational age (weeks)				
<28	1.51	15.1	7	7
≥28				0
Sepsis (during the NICU stay)				
Yes	1.46	14.6	6	6
No				0
Significant cardiac disease				
Yes	2.16	21.6	10	10
No				0
Urine output[a] (ml/kg/h)				
<1.32	1.59	15.9	7	7
≥1.32				0
Serum creatinine[a] (mg/dl)				
≥0.98	4.60	46.0	20	20
<0.98				0
Use of nephrotoxic drugs				
Yes	2.46	24.6	11	11
No				0
Use of furosemide				
Yes	1.96	19.6	9	9
No				0
Use of inotropes				
Yes	3.78	37.8	17	17
No				0

Nephrotoxic drugs included vancomycin or colistin or amphotericin B.
PPV positive pressure ventilation, *NICU* neonatal intensive care unit.
[a]First 12 h post admission in NICU.

S ethi

T ibrewal

A garwal

R alna

Wa Z ir

Risk Factors

≥31.5 → Higher Probability of AKI

S T A R Z

Score	AKI Probability
≤37	<20%
38-42	20-<40%
43-48	40-<60%
49-53	60-<80%
≥54	≥80%

Risk Factors

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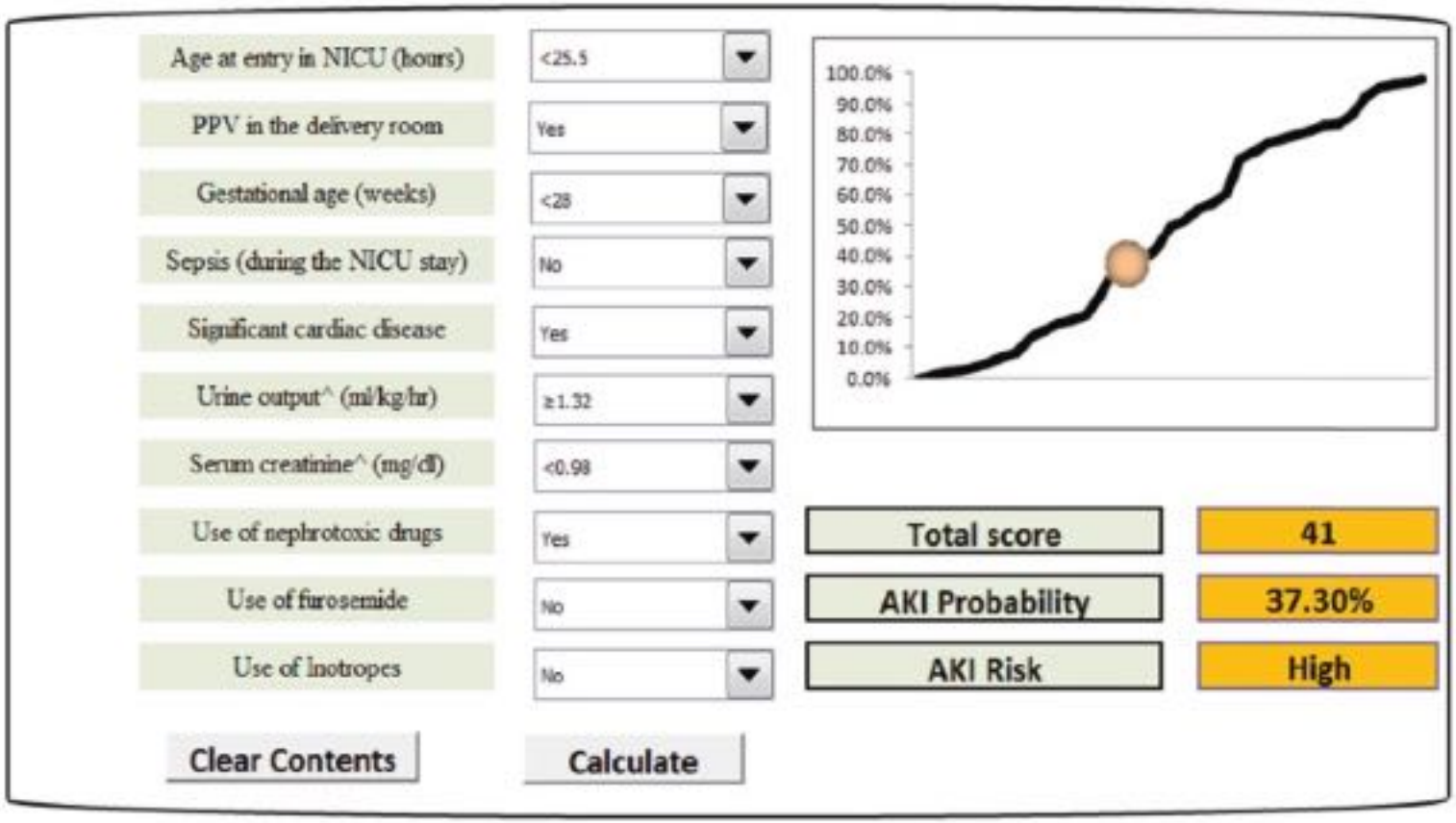

Scoring system dashboard. The scoring system considers variable such as age at entry in the NICU, PPV in the delivery room, gestational age, presence of sepsis and significant cardiac disease, urine output, serum creatinine levels, use of nephrotoxic drugs, furosemide, and inotropes to calculate AKI probability and risk.

The STARZ neonatal score serves to rapidly and quantitatively determine the risk of neonatal AKI

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Evaluation of neonatal AKI

Table 3 Evaluation of a neonate with acute kidney injury

History	Gestational age, birth weight, maternal exposure to nephrotoxic medication Details of perinatal events—fetal heart rate monitoring, Apgar scores and required neonatal resuscitation, medications given Postnatal events—sepsis, nephrotoxic medications, hypotension, other medical conditions with increased incidence of AKI (BPD, CHD, IVH, NEC, PDA), extracorporeal therapies (ECMO)
Physical exam	Focus on volume status and assessment of fluid overload (may require looking at serum electrolytes, intake-output balance, and daily weights for thorough assessment)
Laboratory and imaging	Serum creatinine, blood urea nitrogen, electrolytes Consider urinalysis depending on clinical context Review antenatal kidney imaging if available Consider kidney ultrasound, especially if obstruction is suspected

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1.Adenosine receptor antagonists

Prevent AKI by inhibiting adenosine induced renal vasoconstriction.

1. **Adenosine receptor antagonists**

A. Theophylline

Theophylline may prevent AKI in neonates with *HIE*.

Bellos et al; J Matern Fetal Neonatal Med.(2019)

A single dose of theophylline within the first 6 postnatal hours in newborns with HIE is endorsed in the 2012 KDIGO guidelines to prevent AKI.

Kellum & Lamerie; Crit Care (2013)

1.Adenosine receptor antagonists

B. Caffeine

- **AKI occurred less frequently in VLBW infants and preterm infants <33 weeks' GA who received caffeine within the first postnatal week.**

Chock et al ; J Pediator.2016, Harer et al ; JAMA Pediator 2018.

2. Others

The impact of Erythropoietin on short –and long-term kidney [illegible] outcomes in neonates of extremely low gestational age .Resulted of a multicenter, double-blind, placebo-controlled randomized clinical trial

Askenazi et al ; J Pediatr. 2021.

Failure of remote is chemic preconditioning to reduce the risk of postoperative acute kidney injury in children undergoing operation for complex congenital heart disease: a randomized single center study,

Pedersen et al ; J Thorac Cardiovasc Surg.2012

Effect of intraoperative dexamethasone on major complications and mortality among infants undergoing cardiac surgery: the DECISION randomized clinical trail.

Lomivorotov et al ; JAMA. 2020

Prevention

- **There have been multiple therapeutics evaluated for AKI prevention in neonates (without positive results), including erythropoietin, therapeutic hypothermia, remote ischemic preconditioning, and corticosteroids.**

- **Methylxanthines have been evaluated in multiple neonatal populations and have had promise as a preventive treatment of AKI in high-risk populations.**

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1-Fluid balance

Is

The contribution of medication, "flushes" and feeds

Vital signs assessment

Os

Insensible losses increase with decreasing GA

Hypovolemia
- **Fluid challenge**
- **1-2 ml/kg over 1-2 h**

Hypervolemia
- **Fluid restriction ??**
- **Diuretics**

2- Diuretics

Hypervolemic

Frusemide is a frequently used loop diuretic.

IV dosing : 0.5-1 mg/kg/dose.
Oral dosing : 0.5-2 mg/kg/dose.
Infusion dosing: 0.05-0.4 mg/kg/h

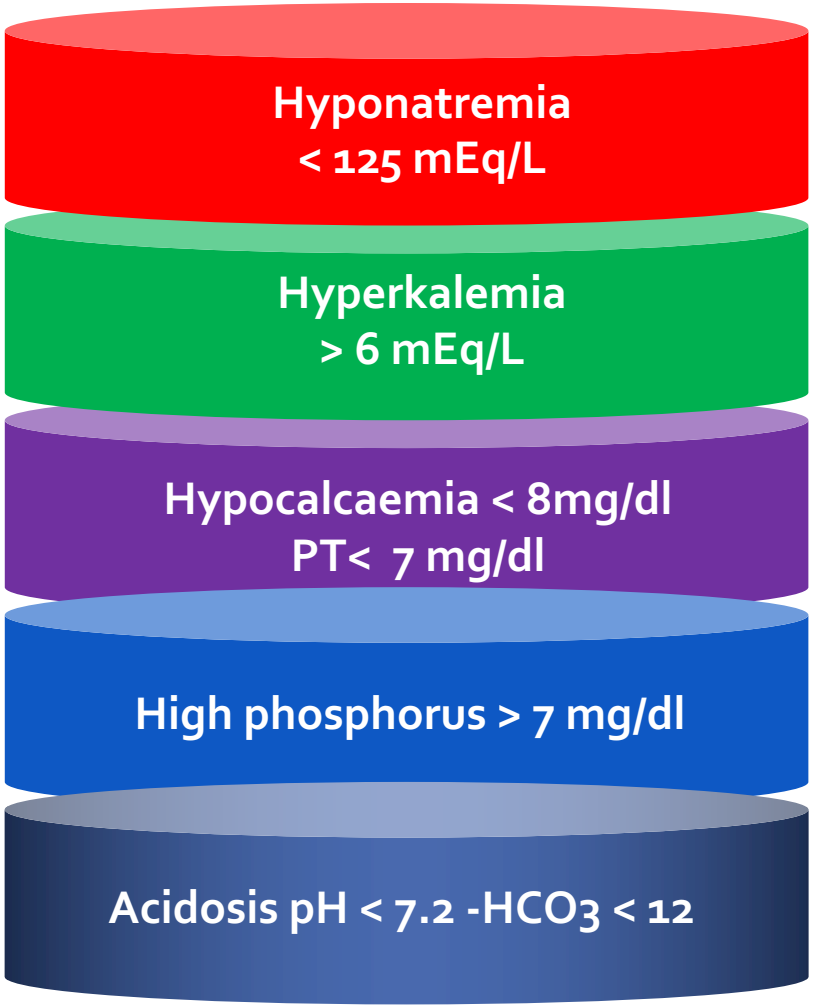
Euvolemic

Furosemide Stress test

Improving urine output with diuretic therapy ***does not*** equate to an improvement in renal function or GFR.

2h-UOP
≤ 1ml/kg

3- Correction of Electrolyte imbalance



4-Renal replacement therapy

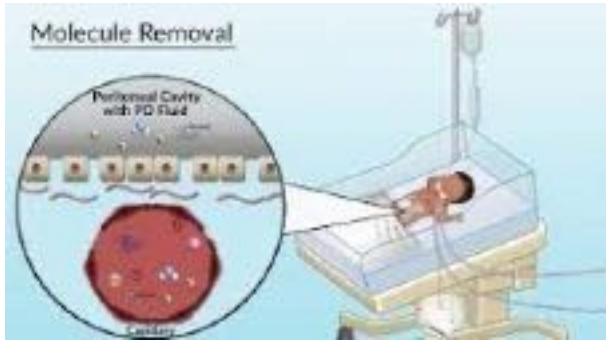
When?

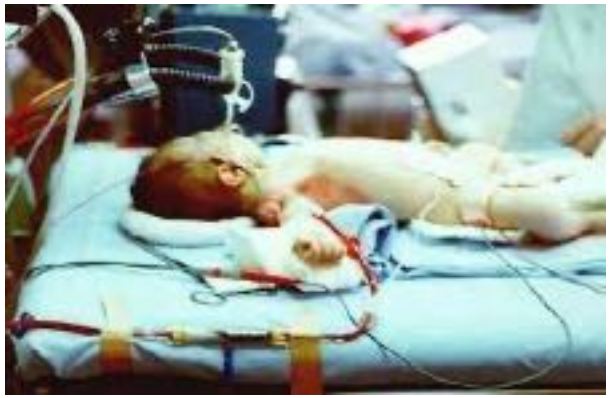
- **Kidney support therapy is rarely considered for early initiation.**

- **Added risk of dialysis machines, ethical considerations, challenges with vascular access, and a lack of evidence on the role of AKI and fluid overload in these patients.**

4-Renal replacement therapy

Modality





Laughon et al., Am J Perinatol. 2015
Semin Fetal Neonatal Med. 2017

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Outcome

1. **Mortality and length of hospital stay**

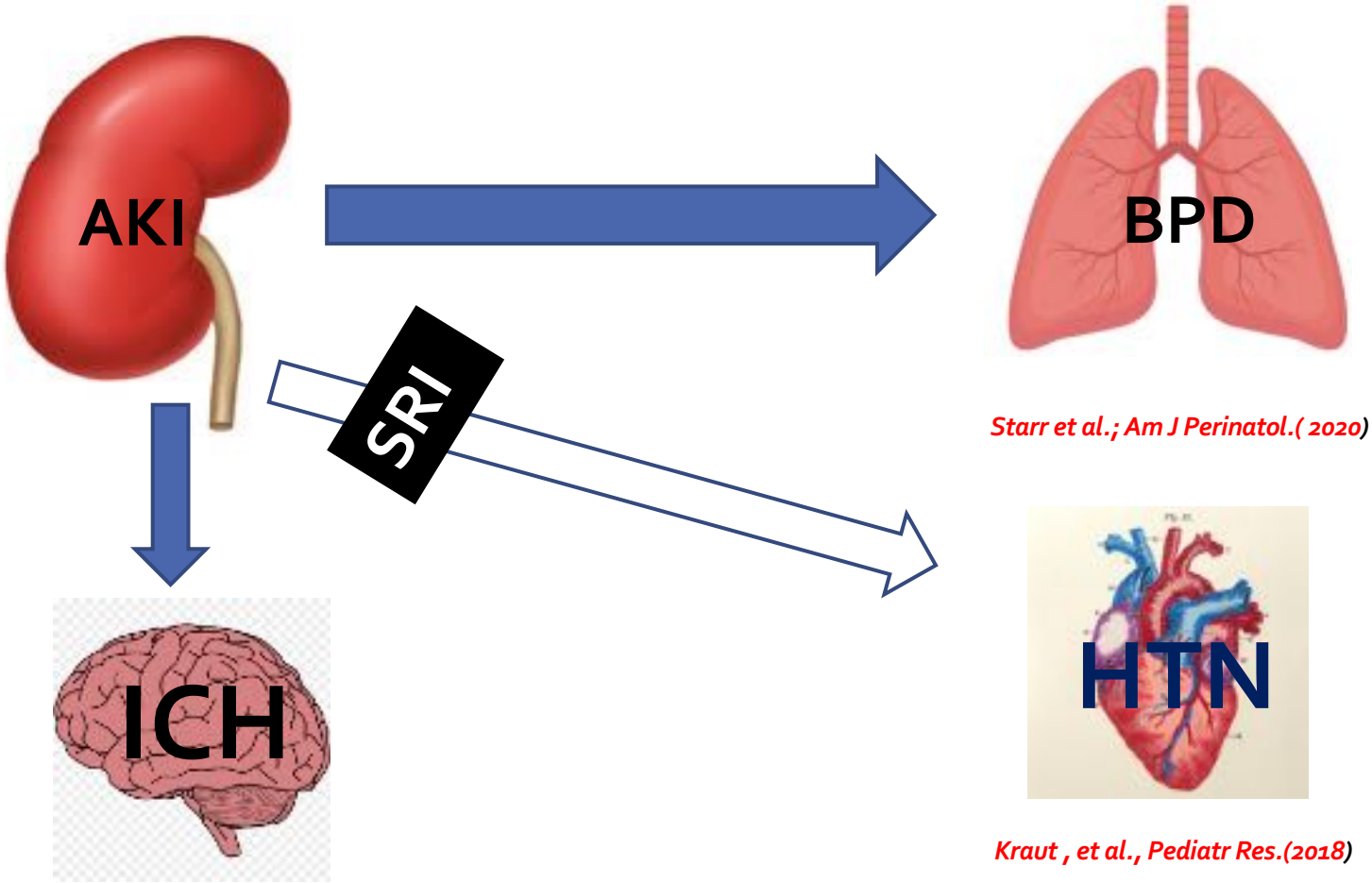
Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study

Jennifer G. Jetton, MD[1], Louis J. Boohaker, MPH[2], Sidharth K. Sethi, MD[3], Sanjay Wazir, MD[4], Smriti Rohatgi, MD[5], Danielle E. Soranno, MD[6], Aftab S. Chishti, MD[7], Robert Woroniecki, MD[8], Cherry Mammen, MD[9], Jonathan R. Swanson, MD[10], Shanty Sridhar, MD[11], Craig S. Wong, MD[12], Juan C. Kupferman, MD[13], Russell L. Griffin, PhD[14], and David J. Askenazi, MD[15,*] on behalf of the Neonatal Kidney Collaborative (NKC)[**]

Outcome

	ANY AKI			AKI MAX Stage				
	NO (n=1417)	YES (n=605)	p-value	0 (n=1417)	1 (n=281)	2 (n=143)	3 (n=181)	p-value
Survived			<0·0001					<0·0001
Yes	1397 (98·6%)	546 (90·3%)		1397 (98·6%)	255 (90·7%)	133 (93·0%)	158 (87·3%)	
No	20 (1·4%)	59 (9·7%)		20 (1·4%)	26 (9·3%)	10 (7·0%)	23 (12·7%)	
LOS (Days)	19 (9, 36)	23 (10, 61)	<0·0001	19 (9, 36)	18 (9, 55)	30 (11, 79)	27 (13, 59)	<0·0001

2. Organ cross talk



Starr et al.; Am J Perinatol.(2020)

Kraut , et al., Pediatr Res.(2018)

Stoops et al., Neonatology (2018)

Outcome

3- CKD

4-55% of PT AKI develop CKD at school age.

9-32% of FT AKI develop CKD at school age.

KDIGO classification schemata for CKD for ages less than 2 years

Neonatal CKD Classification	GFR
Normal GFR	GFR ≤1 SD below the mean
Moderately reduced GFR	GFR >1 SD to ≤2 SD below the mean
Severely reduced GFR	GFR >2 SD below the mean

Abbreviations: KDIGO, Kidney Disease: Improving Global Outcomes; SD, standard deviation.

Adapted from Kidney Disease: Improving Global Outcomes (KDIGO) 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International Supplements 2013;3(1). Jan 1; with permission.

LOGO

- Accurate recognition of neonatal AKI requires an understanding of the physiology of maturation of GFR and tubular function and careful attention to the nuances that differentiate neonatal from pediatric AKI KDIGO definitions (namely the use of a reference serum creatinine).

- Evaluation of a neonate with acute kidney injury begins with careful evaluation of prenatal and perinatal history and includes a physical examination with particular attention to fluid overload assessment, augmented by laboratory testing and selected imaging.

- Management of AKI focuses primarily on avoidance of fluid overload and amelioration of worsening AKI.

- Diuretics may be helpful in preventing fluid overload or correcting electrolyte disturbances but do not appear to change the trajectory of AKI.

- If kidney support therapy is required for management of AKI or fluid overload, both PD and CRRT can be used.

- Neonates with AKI are at increased risk of CKD and hypertension in childhood and adulthood.

Questions

2) Factors that increase the risk of AKI in neonates include all except:

- a. Low birth weight.
- b. Maternal exposure to nonsteroidal anti-inflammatory drugs (NSAIDs).
- c. Spontaneous vaginal delivery.
- d. Congenital heart disease in the baby.

Questions

3) Which is a true statement regarding limitations of serum creatinine?

- a. Serum creatinine is a marker of tubular injury.
- b. It is affected by the volume status and may be diluted in conditions of fluid overload.
- C. Baseline serum creatinine is established in neonates by day of life 7
- d. All neonates have the same baseline.

Questions

4) What is the most common long-term outcome of acute kidney injury?

- a. Normal kidney function throughout childhood without kidney-related complications.
- b. Ongoing CKD at NICU discharge requiring outpatient management.
- c. Stage 5 chronic kidney disease during childhood.
- d. Improvement in serum creatinine to baseline during hospitalization but mild chronic kidney disease and/or hypertension during childhood.