Acute renal injury in the neonatal period

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AKI in neonates

Selewski *Pediatrics* 2015

TABLE 1 Neonatal AKI KDIGO Classification

Stage	SCr	Urine Output
0	No change in SCr or rise <0.3 mg/dL	≥ 0.5 mL/kg/h
1	SCr rise ≥ 0.3 mg/dL within 48 h or SCr rise ≥1.5–1.9 × reference SCr[a] within 7 d	<0.5 mL/kg/h for 6 to 12 h
2	SCr rise ≥2.0–2.9 × reference SCr[a]	<0.5 mL/kg/h for ≥ 12 h
3	SCr rise ≥3 × reference SCr[a] or SCr ≥2.5 mg/dL[b] or Receipt of dialysis	<0.3 mL/kg/h for ≥24 h or anuria for ≥12 h

TABLE 2 Risk Factors for AKI in Neonates

Study	Population	Study Size	Risk Factors Associated With AKI
Cataldi et al 2005[48]	Premature infants	172	Low Apgar scores, exposure to ampicillin, ceftazidime, ibuprofen
Cuzzolin et al 2006[47]	Premature infants	246	Maternal nonsteroidal anti-inflammatory drugs during pregnancy, intubation at birth, low Apgar scores, ibuprofen administration to infant
Koralkar et al 2011[10]	VLBW	229	Lower birth weight, lower gestational age, lower Apgar scores, UAC, mechanical ventilation, inotrope support
Viswanathan et al 2012[65]	ELBW	472	High mean airway pressures, lower mean arterial pressures, higher exposure to cefotaxime
Mathur et al 2006[55]	Neonates with sepsis	200	Lower birth weight, meningitis, DIC, and shock
Selewski et al 2013[12]	Asphyxiated neonates undergoing therapeutic hypothermia	96	Asystole at the time of birth, clinical seizures before cooling, persistent pulmonary hypertension, elevated gentamicin or vancomycin levels, pressor support, transfusions
Bruel et al 2013[103]	Premature infants (<33 wk)	1461	Serum sodium variation, PDA, catecholamine treatment, nosocomial infections, BPD, cerebral lesions, neonatal surgery
Gadepalli et al 2011[8]	Congenital diaphragmatic hernia	68	Lower 5-min Apgar score, AKI correlated with left-sided CDH
Bolat et al 2013[54]	General NICU	1992	Pregnancy-induced hypertension, PPROM, antenatal corticosteroids, SGA, birth weight <1500 g, endotracheal intubation, UVC, ibuprofen therapy for PDA closure, sepsis
Askenazi et al 2013[63]	Birth weight >2000 g, gestational age >34 wk, 5-min Apgar <7	58	Lower birth weight, male, lower Apgar scores at 5 min, lower cord pH, mechanical ventilation

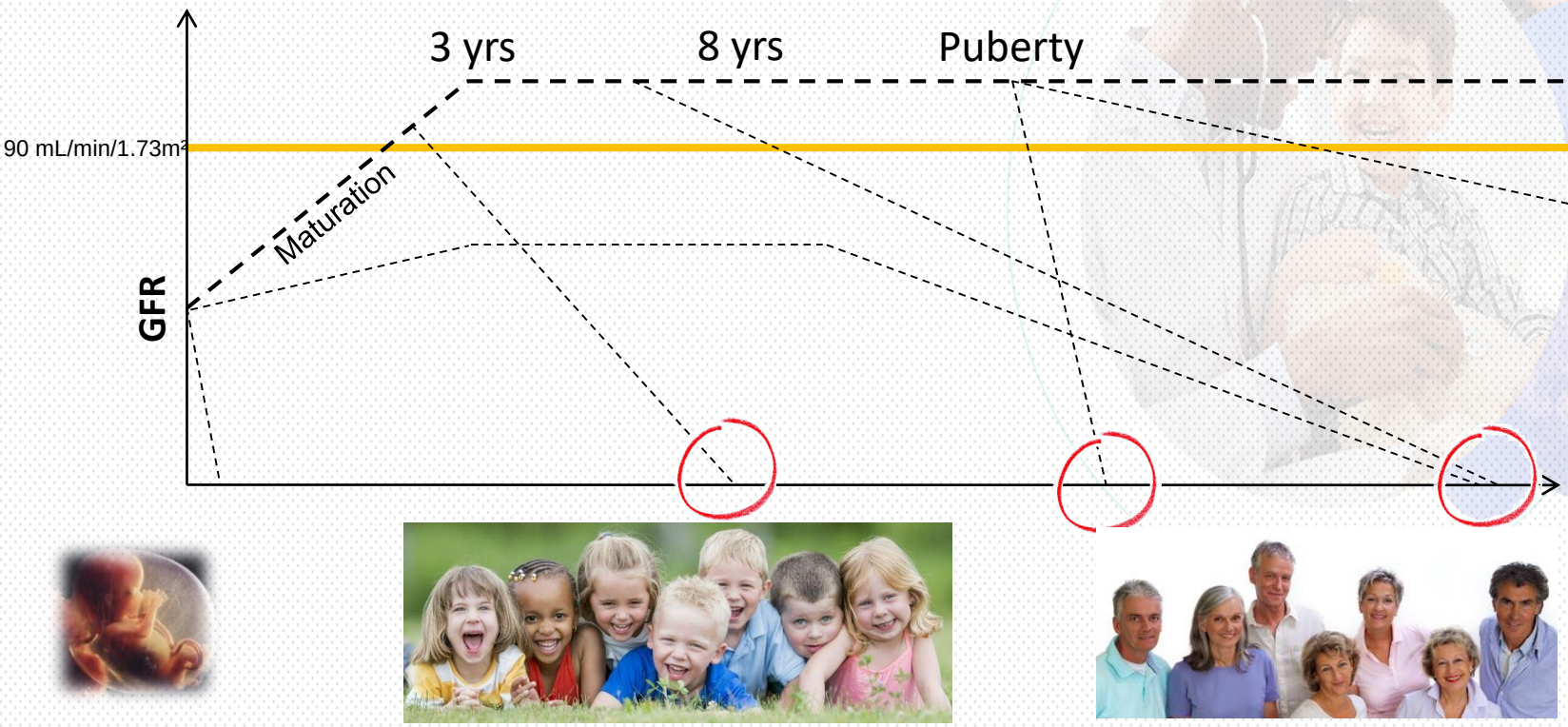
RIFLE score

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					

Ricci *Nephrol Dial Transplant* 2013

A question of renal capital



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Wühl *Pediatr Nephrol* 2008

Fetal programming: glomerular number

Schreuder *Kidney Int* 2007

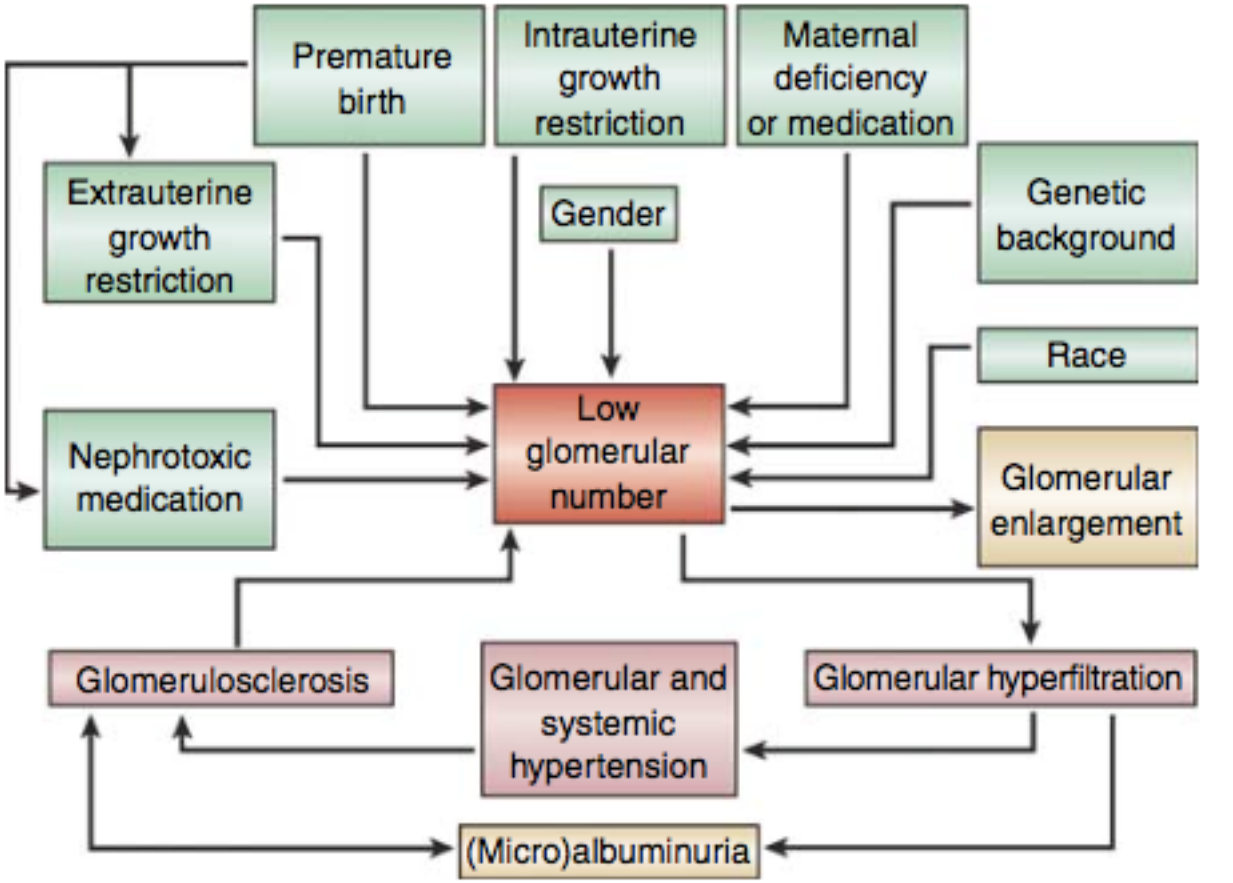


Figure 1 | Integration of renal programming ('Barker' hypothesis) with hyperfiltration hypothesis.

Fetal programming: BP

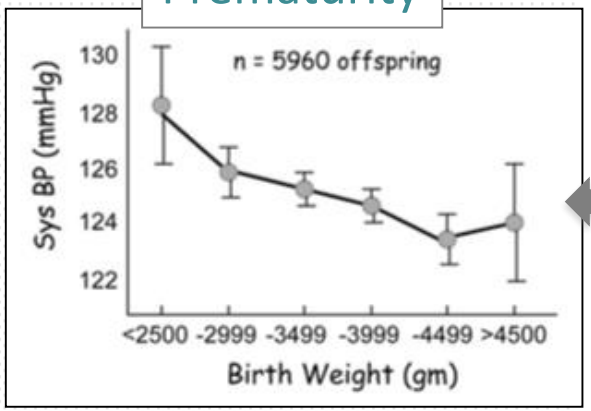
Maternal environment

Maternal Undernutrition
Maternal Glucocorticoids
Maternal Sodium Overload/Low Sodium
Placental Insufficiency

Early Intervention

Early Intervention

Prematurity



Jarvelin *Hypertension* 2004

Low Number of Nephrons

Renal Hemodynamic Alterations ?

Increase Tubular Na^+ Transporters

Increase Renal Oxidative Stress

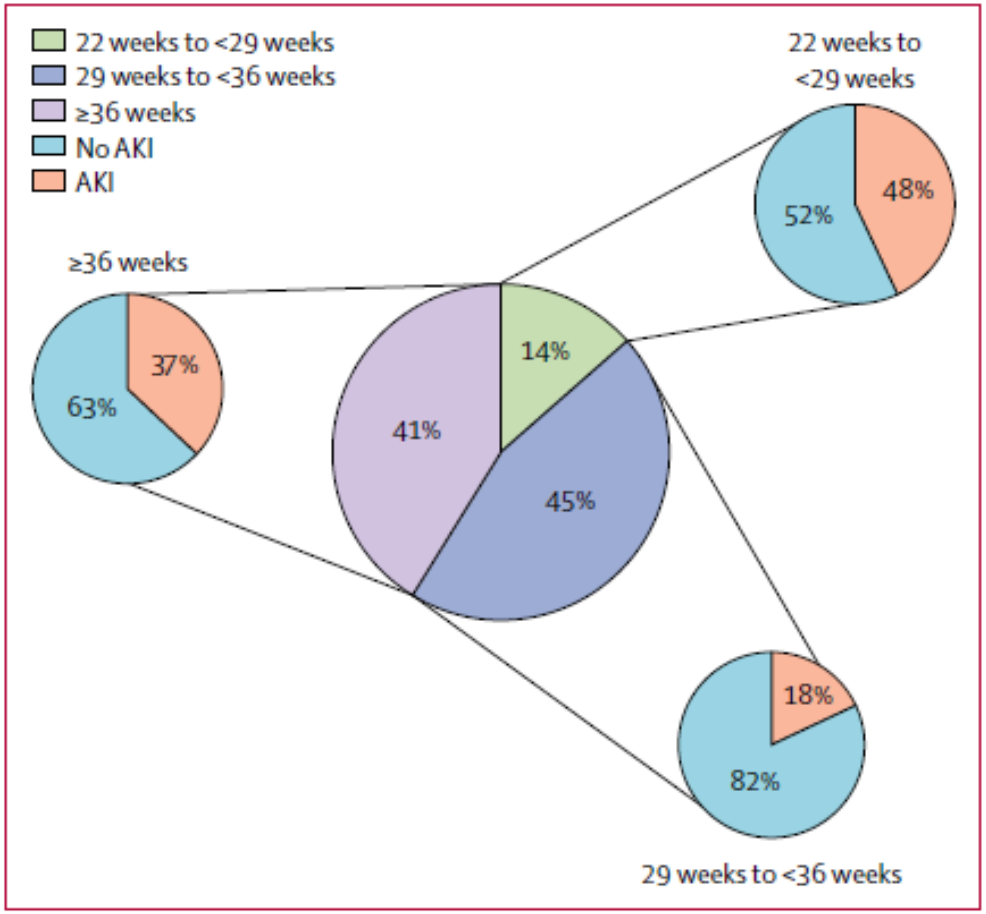
Reduced GFR ?

Increased Na^+ Reabsorption

Hypertension

Paixão *Biol Reprod* 2013

Epidemiology: gestional age distribution and AKI status



AWAKEN study – 2162 critically ill neonates from 24 NICUs
Jetton *Lancet Child Adolesc Health* 2017

Epidemiology: infant variables

	No AKI (n=1417)	AKI (n=605)	p value
Infant variables			
Sex	..	..	0·12
Female	622 (44%)	258 (43%)	..
Male	795 (56%)	347 (57%)	..
Ethnic origin	..	..	0·03
Hispanic	198 (14%)	60 (10%)	..
Non-Hispanic	1004 (71%)	441 (73%)	..
Unknown	215 (15%)	104 (17%)	..
Race	..	..	0·07
White	777 (55%)	364 (60%)	..
Black	271 (19%)	107 (18%)	..
Other	369 (26%)	134 (22%)	..
Site of delivery (outborn)	505 (36%)	349 (58%)	<0·0001
Gestational age	..	..	<0·0001
22 weeks to <29 weeks	142 (10%)	131 (22%)	..
29 weeks to <36 week	748 (53%)	168 (28%)	..
≥36 weeks	527 (37%)	306 (51%)	..
Birthweight (g)	..	..	<0·0001
≤1000	112 (8%)	119 (20%)	..
1001–1500	238 (17%)	57 (9%)	..
1501–2500	552 (39%)	124 (21%)	..
≥2501	513 (36%)	302 (50%)	..
Apgar score	..	..	..
1 min	7·00 (5·00–8·00)	6·00 (3·00–8·00)	<0·0001
5 min	8·00 (7·00–9·00)	8·00 (6·00–9·00)	<0·0001

	No AKI (n=1417)	AKI (n=605)	p value
Infant variables			
Reason for admission*	..	..	
Prematurity <35 weeks	791 (56%)	263 (43%)	<0·0001
Respiratory symptoms	314 (22%)	150 (25%)	0·20
Respiratory failure	651 (46%)	281 (46%)	0·84
Sepsis evaluation	742 (52%)	274 (45%)	0·004
Hypoxic ischaemic encephalopathy	70 (5%)	48 (8%)	0·01
Seizures	33 (2%)	37 (6%)	<0·0001
Hypoglycaemia	168 (12%)	50 (8%)	0·02
Hyperbilirubinaemia	32 (2%)	29 (5%)	0·002
Metabolic evaluation	8 (1%)	12 (2%)	0·003
Trisomy 21	14 (1%)	9 (1%)	0·33
Congenital heart disease	34 (2%)	48 (8%)	<0·0001
Necrotising enterocolitis	6 (<1%)	15 (2%)	<0·0001
Omphalocele and gastroschisis	32 (2%)	15 (2%)	0·76
Need for surgical evaluation	47 (3%)	48 (8%)	<0·0001
Meningomyelocele	9 (1%)	8 (1%)	0·12
Small for gestational age	306 (22%)	117 (19%)	0·27
Large for gestational age	58 (4%)	40 (7%)	0·02

AWAKEN study – 2162 critically ill neonates from 24 NICUs
Jetton *Lancet Child Adolesc Health* 2017

Definition

Decrease in GFR

- Plasma creatinine
  - Late (50 % nephron loss)
  - Overestimation
  - Which method? (interférence)
  - When?
- Clearance measurement
- Estimation formulas
  - Which K?
  - Indivudual *vs*. population?
- New markers
  - Cystatine C
  - Others?

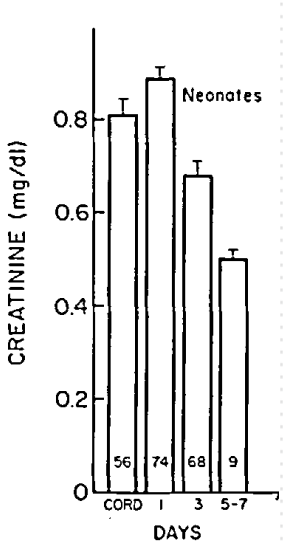
Urine output

- Maintaining homeostasis…
- 99 % 1st micturition <48 h
- 1st urine
  - Low concentration capacity
  - Solute losses
- Variable urine output
- In case of anuria
  - Prenatal information?
  - Obstruction?
  - AKI?
  - Just wait?

Plasma creatinine

Gouyon *Pediatr Nephrol* 2000
Schwartz *J Pediatr* 1984
Selewski *J Pediatr* 2013

- Full-term baby
  - PCr <15 mg/L *[<133 µmol/L]*
  - Decrease over 5 days

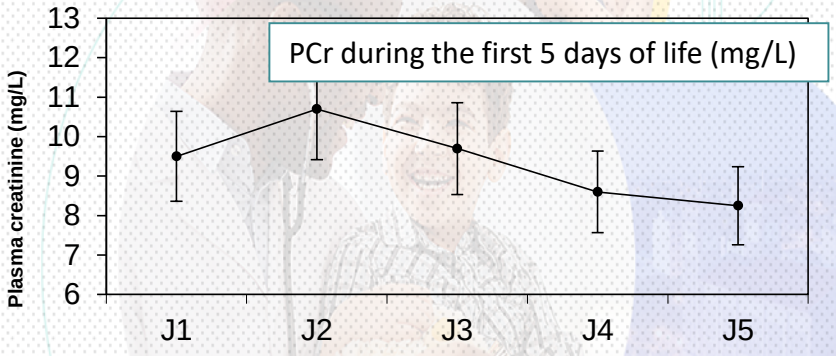


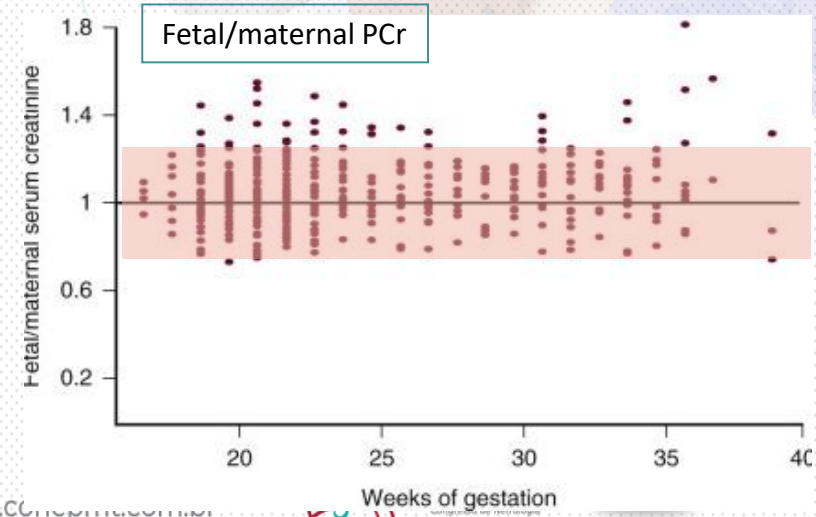
- Premature baby
  - Tubular reabsorption of creatinine
  - Increased PCr in very LBW
  - Decrease over 2 to 3 weeks

Evolution of PCr, µmol/L

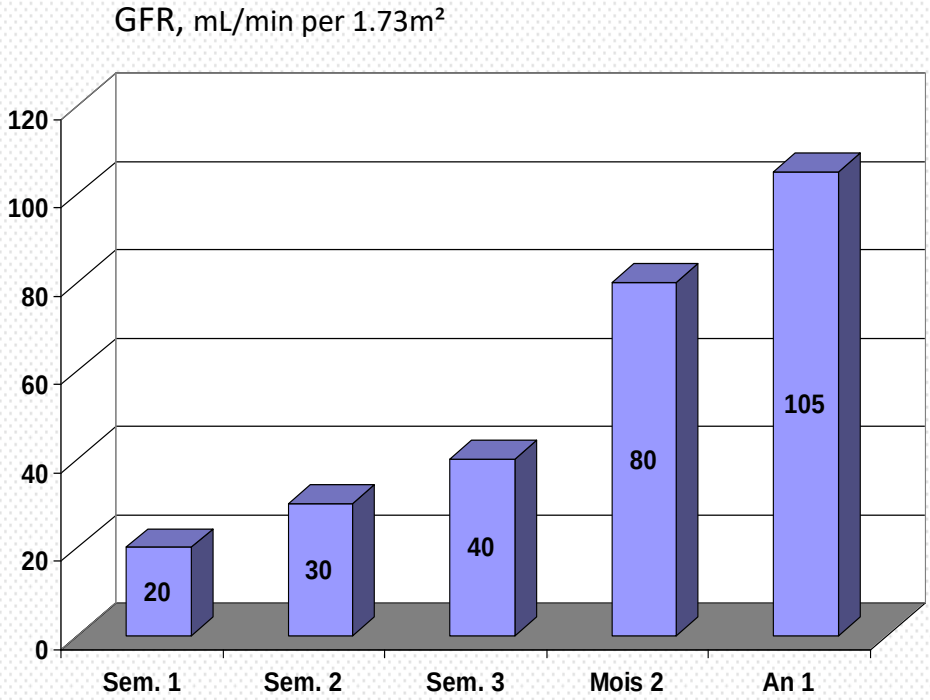
Birth weight	1-2 days	8-9 days	15-16 days	22-23 days
1001-1500 g	95 ±5	64 ±5	49 ±4	35 ±3
1501-2000 g	90 ±5	58 ±7	50 ±8	30 ±2
2001-2500 g	83 ±5	47 ±8	38 ±8	30 ±10
Full-term	66 ±3	40 ±4	30 ±8	27 ±7

Influence of maternal PCr





GFR maturation



Handbook of Pediatric Nephrology *ESPN* 2003

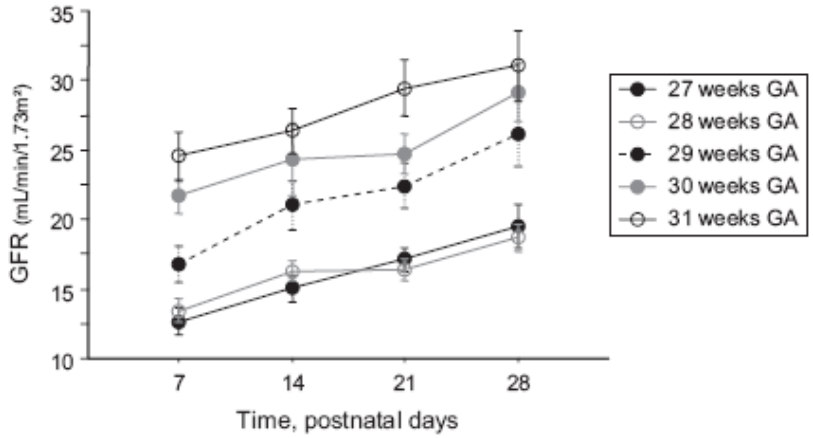


FIGURE 1
GFR according to GA in the first month of life ($n = 275$). Data are means ± SEM.

Vieux *Pediatrics* 2010

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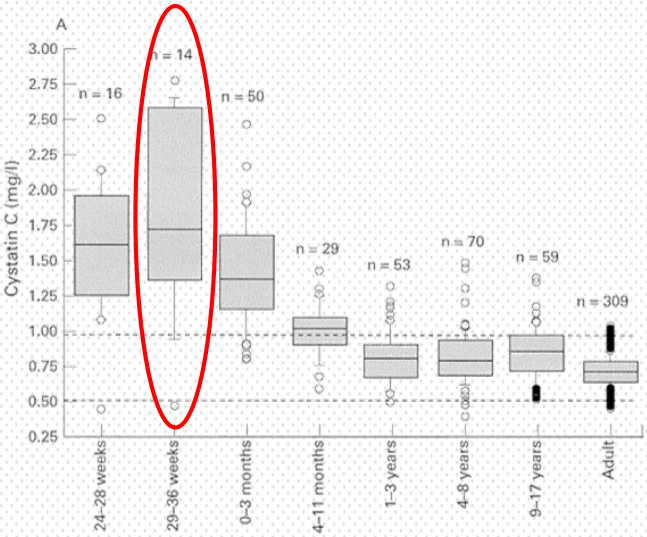
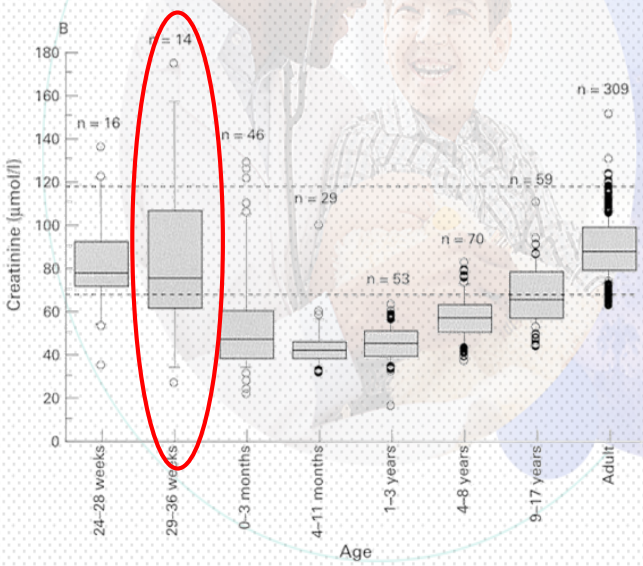
Plasma cystatin C *vs*. Plasma creatinine?

Plasma cystatin C

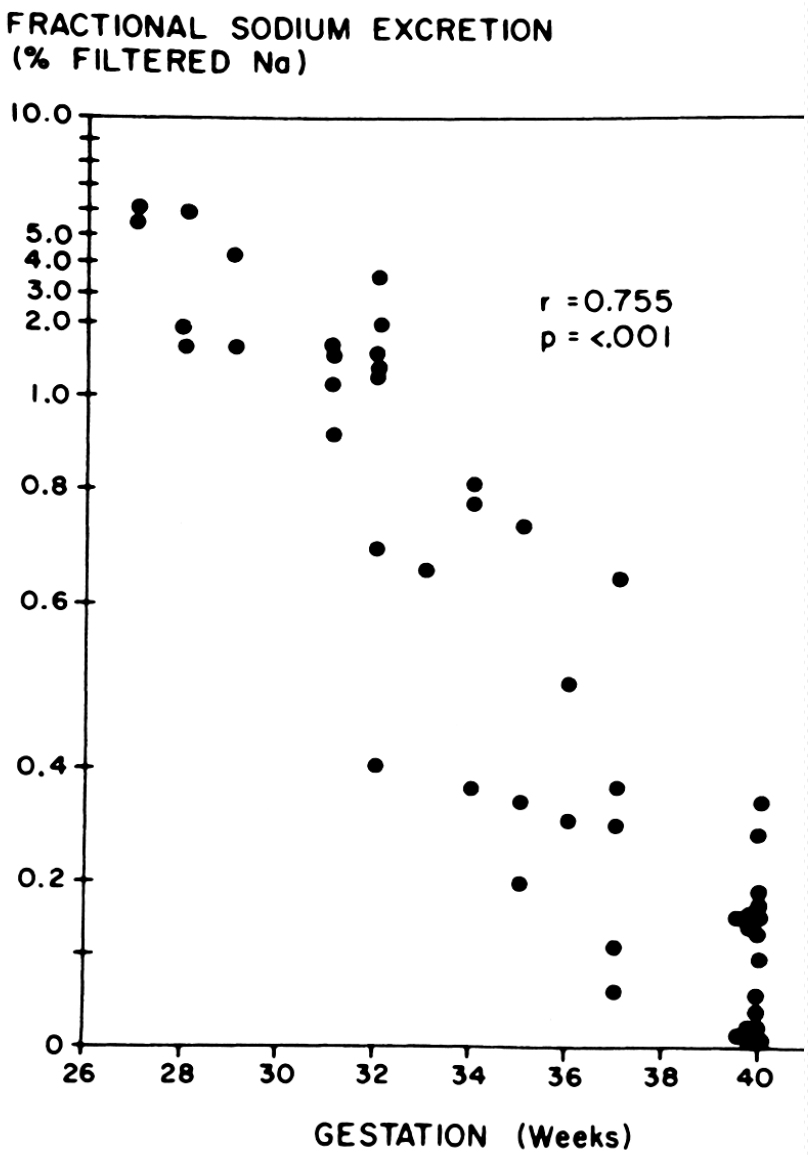


Plasma creatinine



Finney *Arch Dis Child* 2000

Tubular maturation



Excreted fraction of sodium

FeNa (%) = (PCr*UNa/PNa*UCr)*100

Inverse correlation with gestational age

Siegel *Acta Paediatr Scand* 1976

What about other markers to predict AKI?

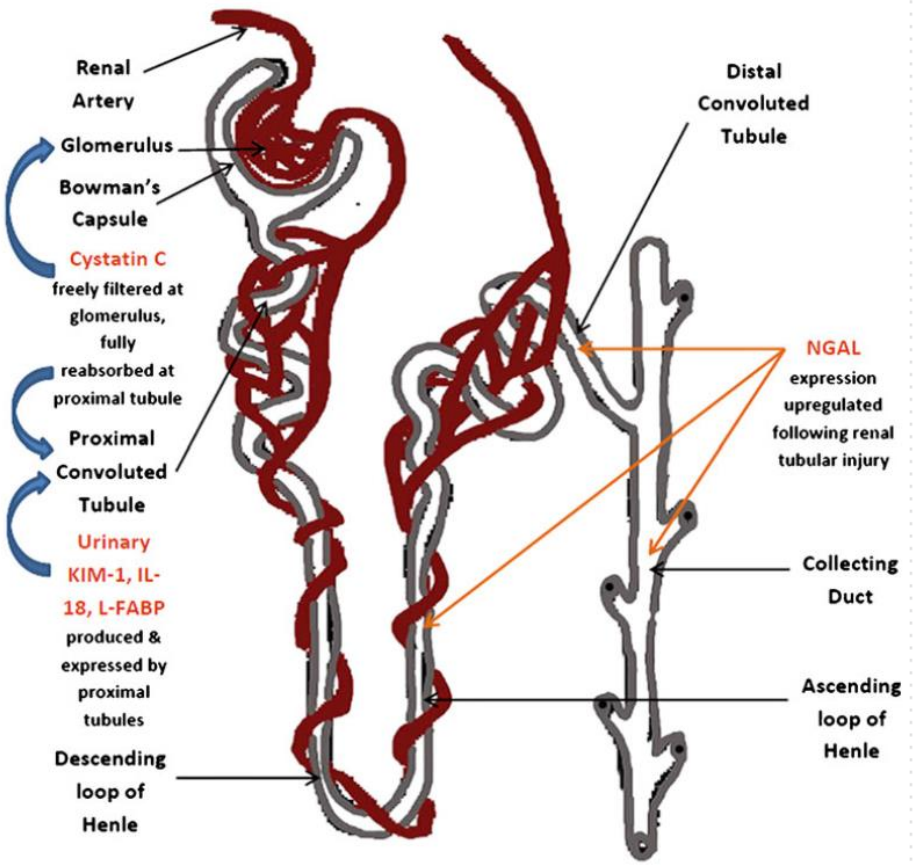


Table 5 Diagnostic accuracy of the biomarkers evaluated on day of life 1 for predicting acute kidney injury (AKI)

	AUC	*p* value	Cut-off point	Sensitivity	Specificity
Serum					
CysC (mg/l)	0.731	0.067	>2.87	66.7	88.5
NGAL (ng/ml)	0.942	<0.001	>89.6	100	92.3
Urine					
Standardized values					
CysC (ng/mg)	0.927	<0.001	>476	100	83.3
NGAL (ng/mg)	0.896	<0.001	>39.3	100	83.3
KIM-1 (ng/mg)	0.608	0.459	>0.928	80	62.5
Absolute values					
CysC (ng/ml)	0.937	<0.001	>204.4	100	91.7
NGAL (ng/ml)	0.865	<0.001	>18.61	100	83.3
KIM-1 (pg/ml)	0.583	0.575	>569.8	40	86

AUC area under the curve, *uCre* urine creatinine, *Cyst C* cystatine, *NAGL* neutrophil gelatinase-associated lipocalin, *KIM-1* kidney injury molecule-1

Sarafadis *Pediatr Nephrol* 2012

What about other markers to predict AKI?

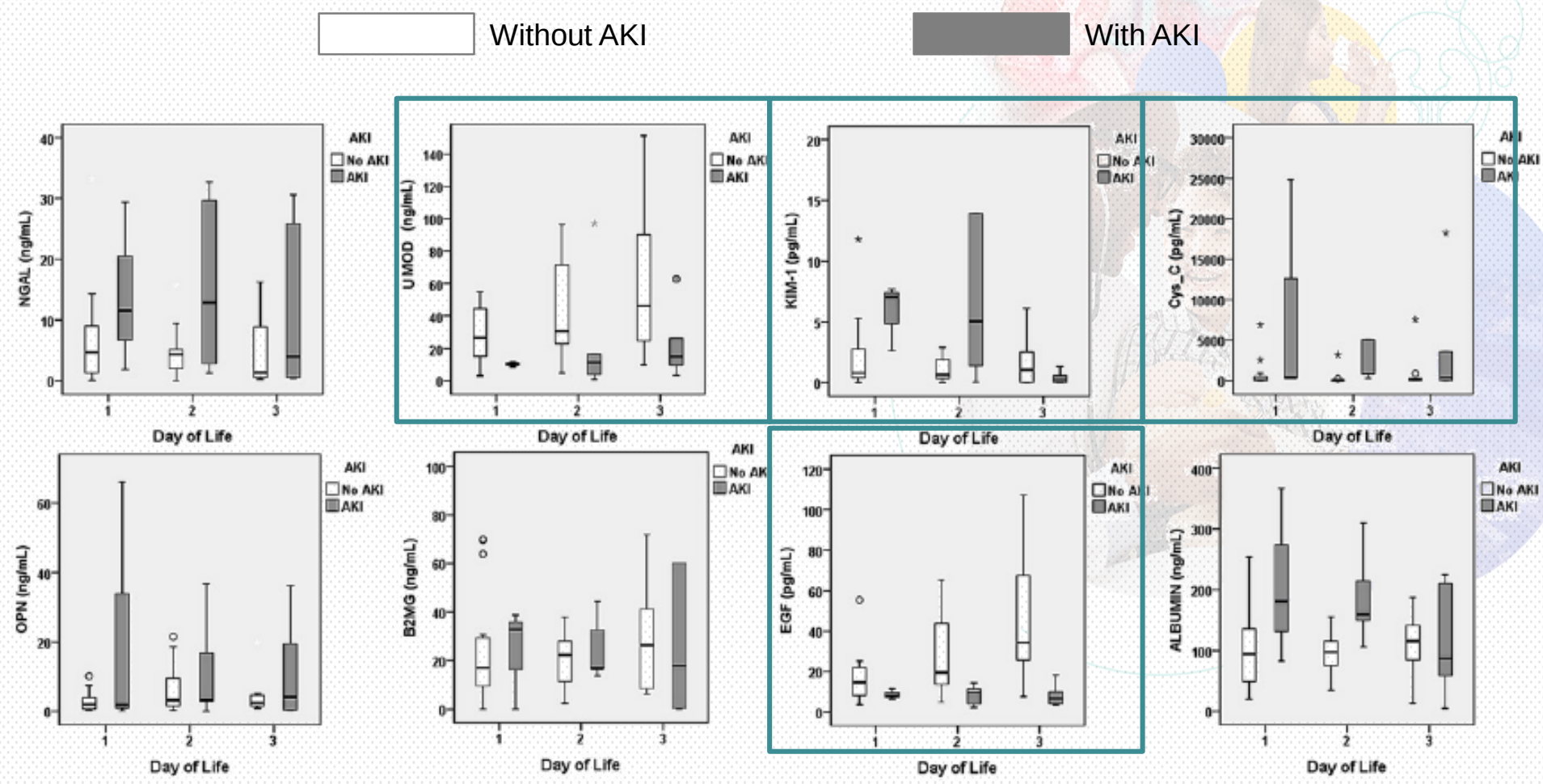


Figure 2. Urine values of NGAL, UMOD, KIM-1, Cys C, OPN, B2mG, EGF, and albumin in infants with AKI (*gray bars*) and infants without AKI (*white bars*) during the first 3 days of life.

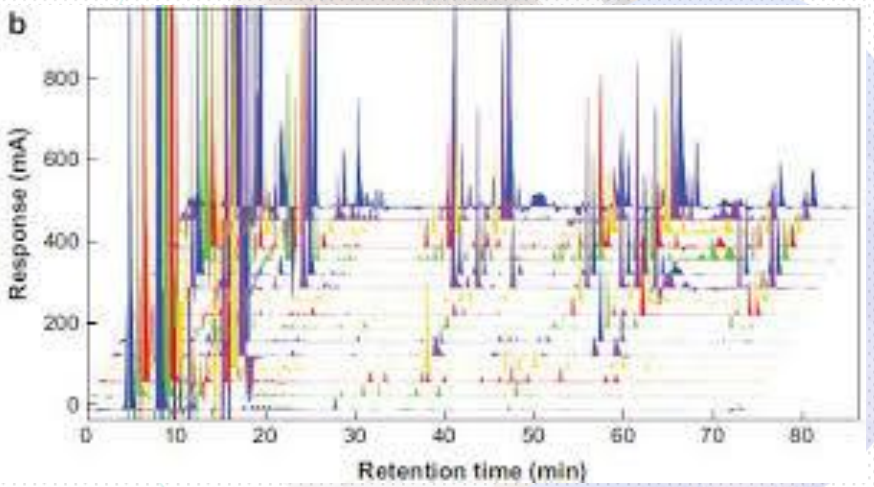
Askenazi *J Pediatr* 2012

Ideal marker

- Very early
- Able to assess short and long-term renal function
- Able to differenciate glomerular and tubular lesions
- Independent of term at the time of diagnosis

In the future: use of metabolomics?

- Individual metabolomic profile
- 20 children with/without AKI
- Hippurate & homovanillate



Kelly Mercier *Pediatr Nephrol* 2016

Diagnosis: Take home message…

What about numbers…

- Plasma creatinine
  - >24h according to mother's PCr
  - Kinetic profile during the first days of life
  - Importance of a « non-decrease » during the first week of life
- Urine output
  - AKI < 0.5 to 1 mL/kg per hour
  - Over which time interval?
  - Delayed 1st micturition
  - Fluctuation over 24h
  - Challenging urine collection

Give priority to global presentation

- Associated metabolic disorders
- At-risk conditions (ductus arteriosus, concomitant treatments, etc.)

Ultrasonography

- Kidney size
- Parenchymal differenciation

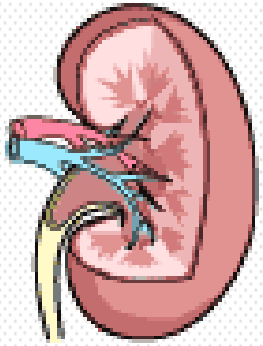
New and forthcoming markers yet to be evaluated/validated

Etiologies

Toth-Heyn *Pediatr Nephrol* 2000

Acute tubular necrosis
Cortical necrosis
Vascular thrombosis
Acute tubulointerstitial nephritis (drugs, viruses)

Neonatal hypoxia
Hypovolemia
Heart failure
Respiratory distress

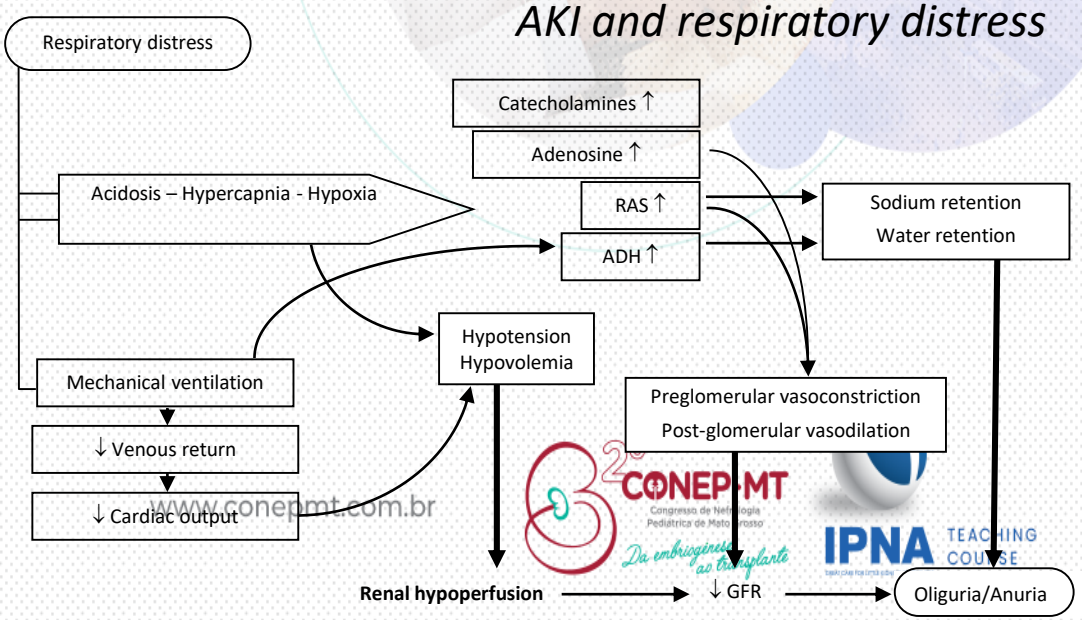


Inherited conditions
Congenital nephropathy
CAKUT

PUV
Obstruction

Predisposition
Genetic polymorphism
IL10-6, IL1b, TNFα, ACE

AKI and respiratory distress



Drug-induced AKI in the neonatal period: NSAIDs

TABLE 3 Common Nephrotoxic Medications in NICU

Drug	Mechanism
Acyclovir	Urinary precipitation, especially with low flow and hypovolemia, with renal tubular obstruction and damage and decreased GFR. May cause direct tubular toxicity (metabolites).
Angiotensin-converting enzyme inhibitors	Decreased angiotensin II production inhibiting compensatory constriction of the efferent arteriole to maintain GFR.
Aminoglycosides	Toxic to the proximal tubules (transport in the tubule, accumulate in lysosome, intracellular rise in reactive oxygen species and phospholipidosis, cell death); intrarenal vasoconstriction and local glomerular/mesangial cell contraction.
Amphotericin B	Distal tubular toxicity, vasoconstriction, and decreased GFR.
Nonsteroidal antiinflammatory drugs	Decreased afferent arteriole dilatation as a result of inhibiting prostaglandin production resulting in reduced GFR.
Radiocontrast agents	Renal tubular toxicity secondary to increase in reactive oxygen species; intrarenal vasoconstriction may play a role.
Vancomycin	Mechanism of AKI unclear, possible mechanism includes proximal tubular injury with generation of reactive oxygen species.

Selewski *Pediatrics* 2015

Table 3 Descriptive and bivariate analysis of the drugs prescribed during the first week of life

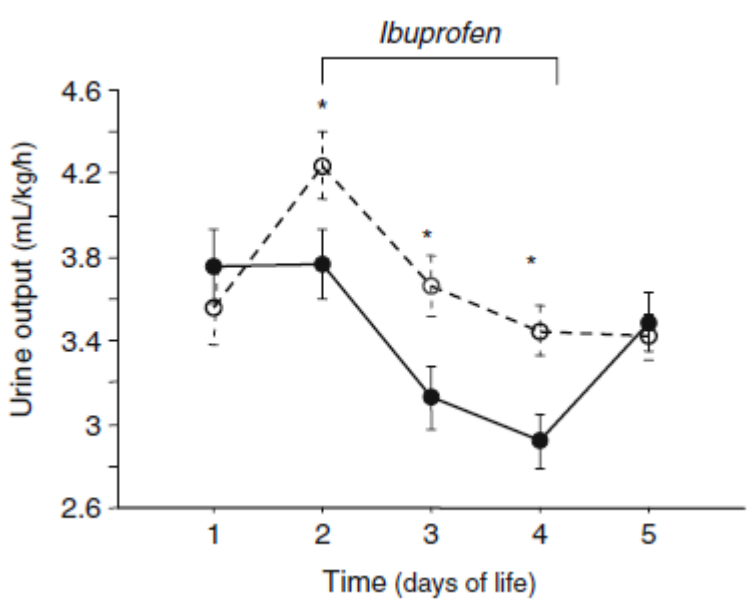
	Low GFR (n=183)	High GFR (n=86)	p
Ibuprofen	55 (30.0%)	15 (17.4%)	0.03
Vasoactive drugs	37 (20.2%)	17 (19.8%)	0.93
Expansion fluids	50 (27.3%)	26 (30.2%)	0.62
Aminoglycosides > 2 days	48 (26.2%)	26 (30.2%)	0.49
Mean plasma amikacin level (mean± SD)	5.3±1.9	4.8±1.8	0.27
High serum level of aminoglycosides (>5 μg/ml)	24 (13.1%)	9 (10.5%)	0.38
Glycopeptides > 2 days	18 (9.8%)	10 (11.6%)	0.65
Mean plasma glycopeptide level (mean±SD)	25.7±8.1	26.6±8.4	0.77
High serum level of glycopeptides (>30 μg/ml)	10 (5.5%)	3 (3.5%)	0.50
Aminoglycosides + glycopeptides	6 (3.3%)	4 (4.7%)	0.58
Cox inhibitors + aminoglycosides	11 (6.0%)	4 (4.7%)	0.65
Cox inhibitors + glycopeptides	11 (6.0%)	3 (3.5%)	0.38
Potentially nephrotoxic drugs	145 (79.2%)	69 (80.2%)	0.85
Nephrotoxic drugs > 2 days	96 (52.5%)	40 (46.5%)	0.36

Vieux *Pediatr Nephrol* 2010

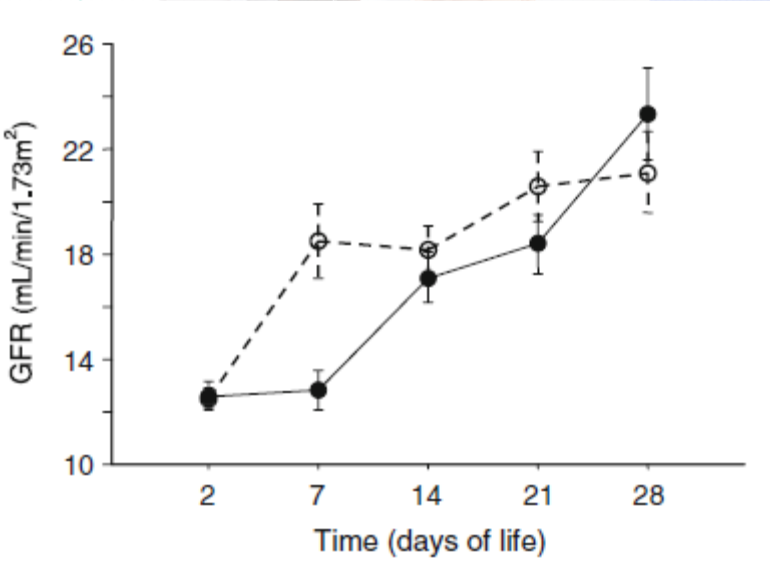
Drug-induced AKI in the neonatal period: NSAIDs

○ Controls ● Ibuprofen

Urine output

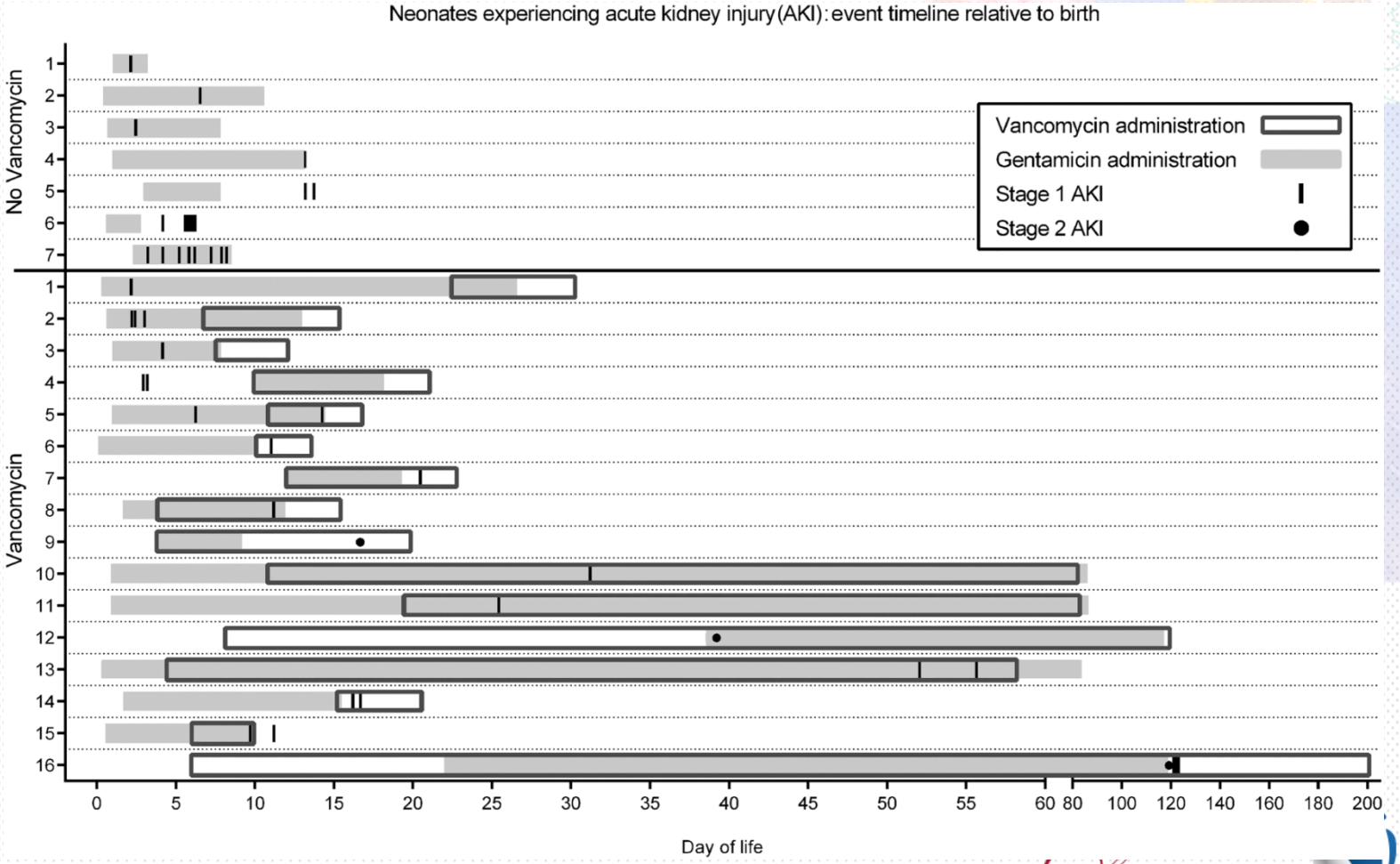


GFR



Vieux *Pediatr Nephrol* 2010

Drug-induced AKI in neonates: Vancomycin and Gentamicin



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Constance *Arch Dis Child Fetal Neonatal Ed* 2015

Primary disease in patient starting RRT in the 1st month of life

Diagnosis (N= 264)	*N*	*%*
CAKUT	144	54.6
Cystic kidney disease	35	13.3
Cortical necrosis	30	11.4
Congenital nephrotic syndrome	15	5.7
Renal vascular disease	9	3.4
Hemolytic uremic syndrome	3	1.1
Angiotensin-receptor blockade fetopathy	3	1.1
Oxalosis	2	0.8
Other not specified	23	8.7

Van Stralen *Kidney Int* 2014

Management

Seminars in Fetal & Neonatal Medicine 2006

Prevention!

- Recognize at-risk situations
- *Primum non nocere*
  - Nephrotoxic drugs
- Clinical assessment of pre-renal condition
  - In/out volumes ml *[poids]*
- Management of shock/hypovolemia
  - 0,9% saline 20mL/kg over 20 min: result?
  - ± Noradrenaline? Dopamine? Corticosteroids?
  - Diuretics?
- Correction of acidosis, both metabolic and respiratory
- Electrolytic disturbances
  - Hyponatremia
  - Hyperkalemia
- Nutrition
- Extrarenal support

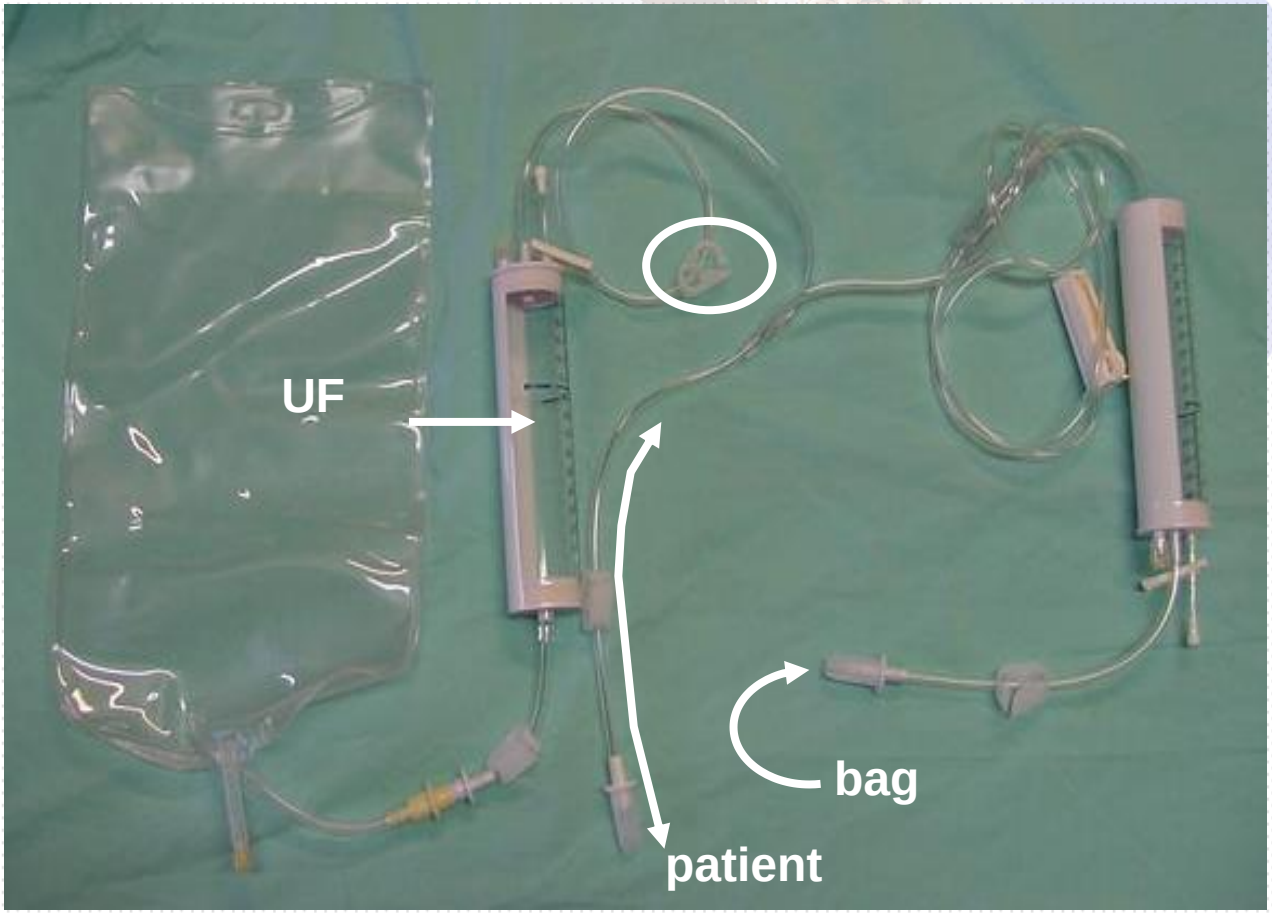
Peritoneal dialysis

- Simple technique
- No vascular access, PD catheter at bedside if required
- Stable BP

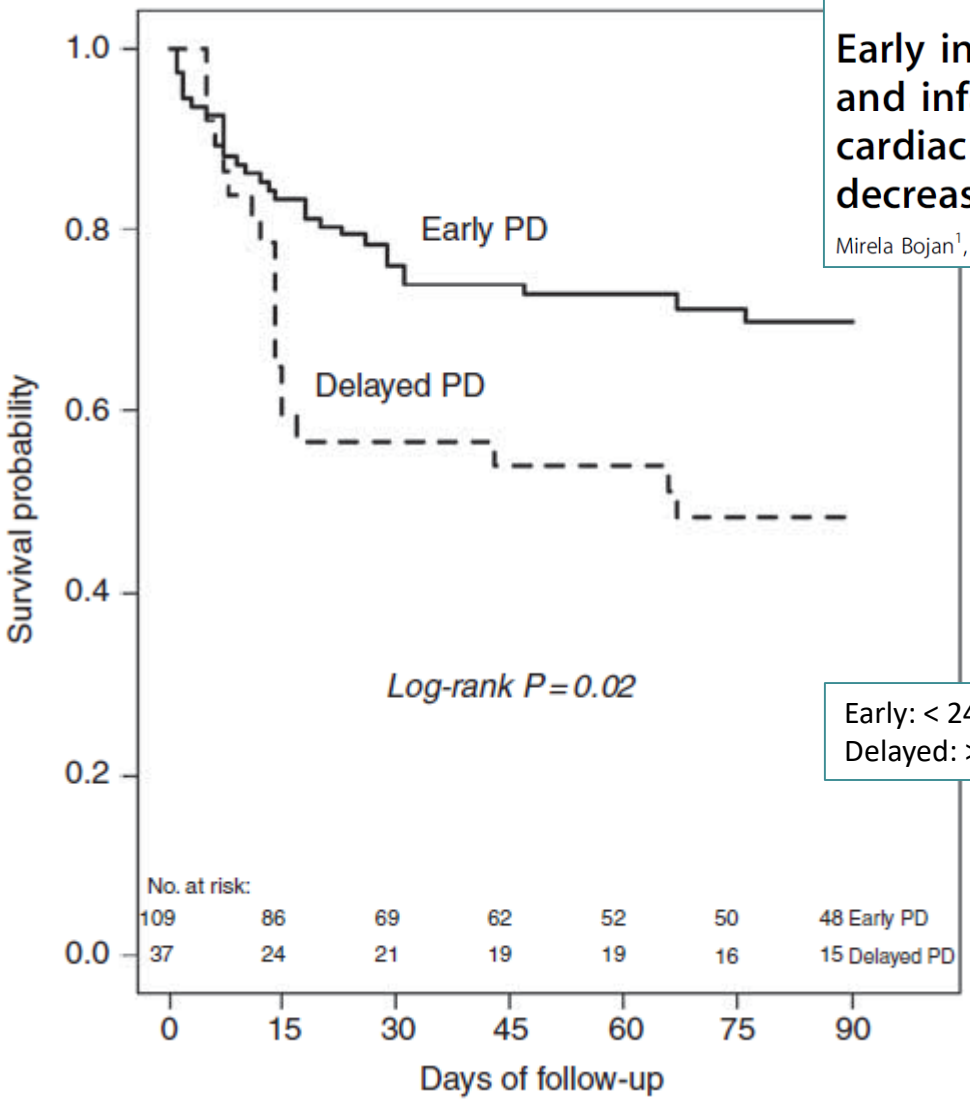
- Automated device
- Home treatment

- Relies on experience
- Risk of peritonitis

- Global challenge
- Ethical issues



Peritoneal dialysis



original article http://www.kidney-international.org

Early initiation of peritoneal dialysis in neonates and infants with acute kidney injury following cardiac surgery is associated with a significant decrease in mortality

Mirela Bojan[1], Simone Gioanni[1], Pascal R. Vouhé[2,3], Didier Journois[3,4] and Philippe Pouard[1]

Early: < 24 hours following surgery
Delayed: > 24 hours following surgery

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HD – CRRT

Period	Year
Technology and bioengineering (I)	1982
Technology and bioengineering (II)	1986
The birth of critical care nephrology	1994
The concept of CRRT dose	2001
AKI awareness	2004
WAK, MOST, and cardiorenal syndrome	2007
The CARPDIEM project (phase I)	2010
The CARPDIEM project (phase II)	2011
The CARPDIEM project (phase III)	2013

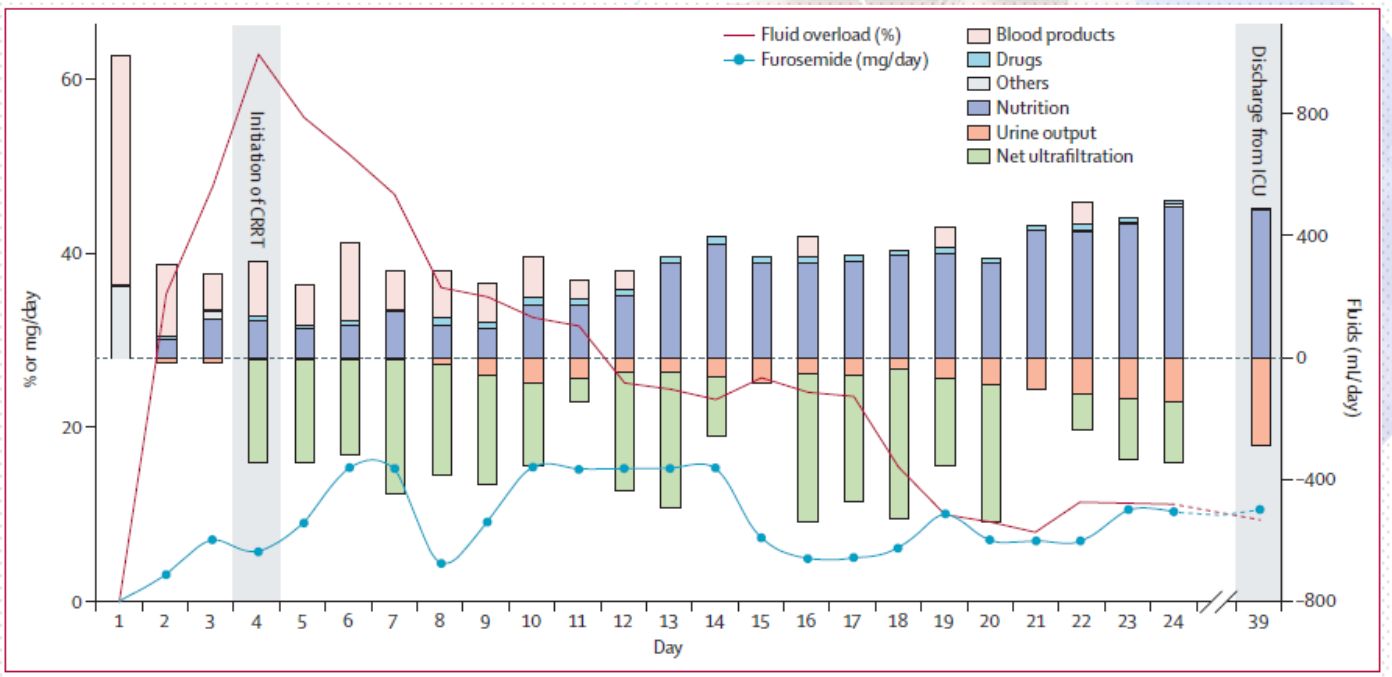


Figure 1: Fluid balance during the first 25 days (and final day) of stay in neonatal intensive care

www.conepmt.com.br

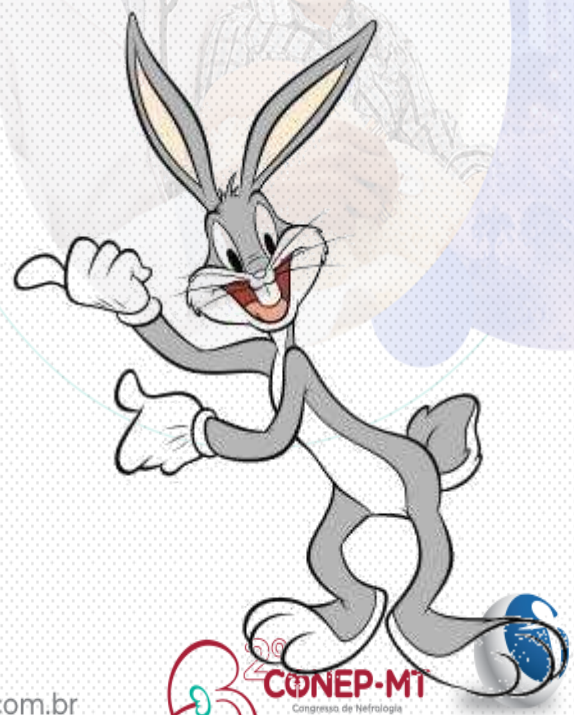
Ronco *Lancet* 2014

Ronco *Am J Kidney Dis* 2015

Other options and future developments

- New/revisited approaches
  - Theophylline (0.5-8 mg/kg) [adenosine antagonist]
  - Anti-thromboxane receptor
  - Calcium channel inhibitors
  - ATP-$MgCl_2$ *(prevention of cell damage)*
  - Thyroxine *(↑ATP)*
  - Cytokines

- Ischemia-reperfusion
  - Stem cells



A randomized, placebo-controlled trial of the effect of theophylline in term neonates with perinatal asphyxia

Bhat *J Pediatr* 2006

30 Placebo *vs*. 40 Theophylline

Single dose, 8 mg/kg

Increased urine output from D2 to D5

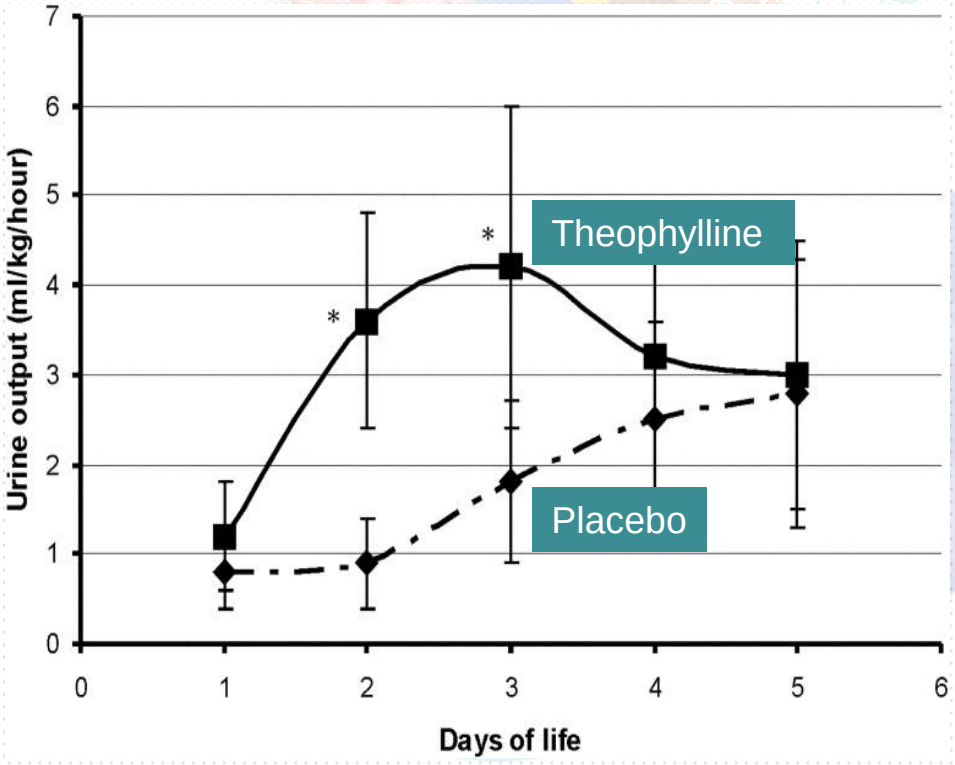
Increased GFR from D2 to D3

20±8 *vs* 7±4; p < 0.001

Severe renal dysfunction

25 % *vs* 60 %

Decreased β2M excretion



But PCr and eGFR comparable at 1 year

Dopamine

Cochrane Database of Systematic Reviews 2007

There is no evidence from randomized trials to support the use of dopamine to prevent renal dysfunction in indomethacin-treated preterm infants (Barrington K, Brion LP)

There is currently insufficient evidence from randomised controlled trials that the use of dopamine in term infants with suspected perinatal asphyxia improves mortality or long-term neurodevelopmental outcome (Hunt R, Osborn D)

Outcomes

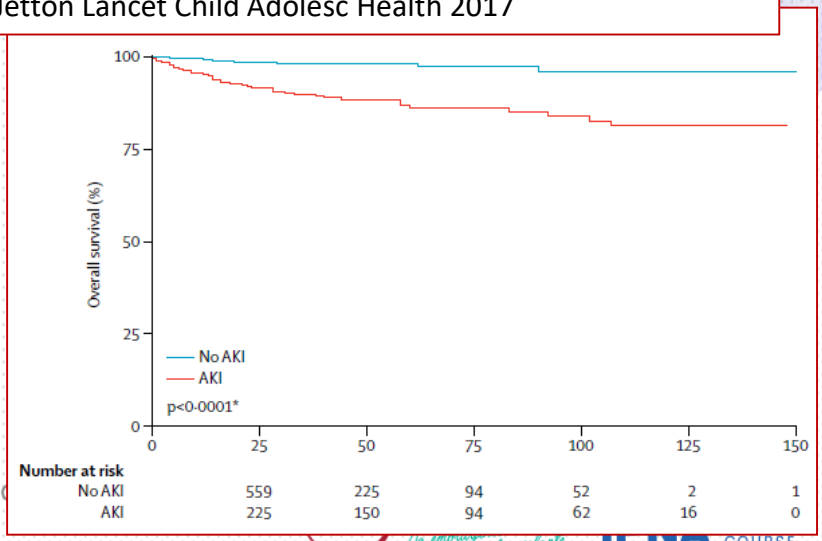
- Better survival in the absence of oliguria/anuria
- Mortality rate increased by 25 to 68 % in case of oliguria/anuria

	Any AKI			Maximum AKI 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 (99%)	546 (90%)	..	1397 (99%)	255 (91%)	133 (93%)	158 (87%)	
No	20 (1%)	59 (10%)	..	20 (1%)	26 (9%)	10 (7%)	23 (13%)	
Length of stay (days)	19 (9–36)	23 (10–61)	<0·0001	19 (9–36)	18 (9–55)	30 (11–79)	27 (13–59)	<0·0001

Data are n (%) or median (IQR). 140 enrolled patients had less than two serum creatinine measurements and no urinary output data. Among patients who did not die, 306 were transferred for convalescence or escalation of care. AKI=acute kidney injury.

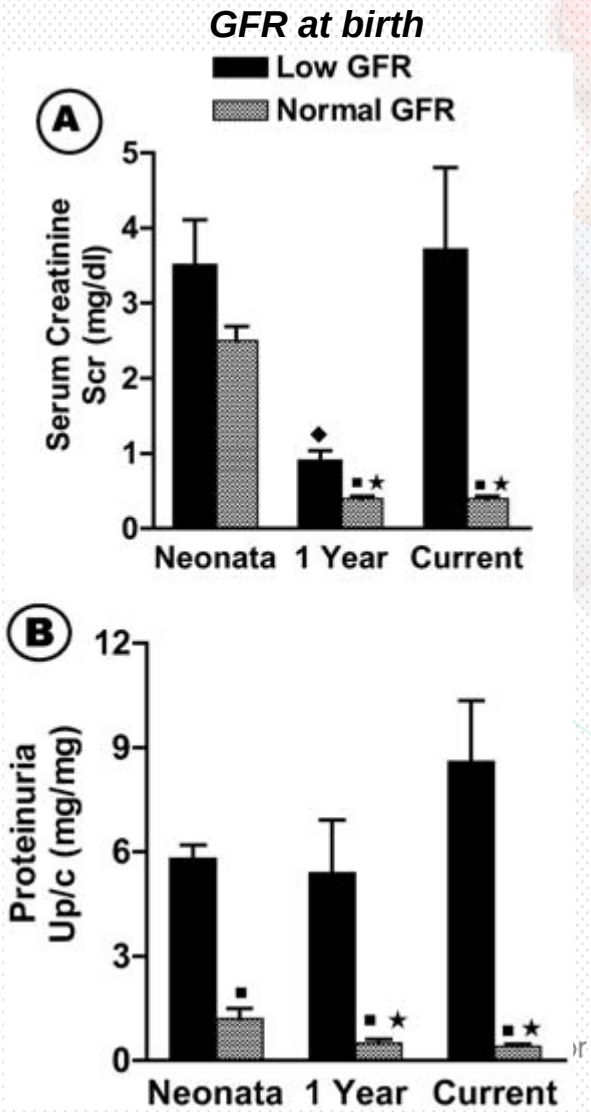
***Table 2*: Clinical outcomes by AKI status**

AWAKEN study – 2162 critically ill neonates from 24 NICUs
Jetton Lancet Child Adolesc Health 2017



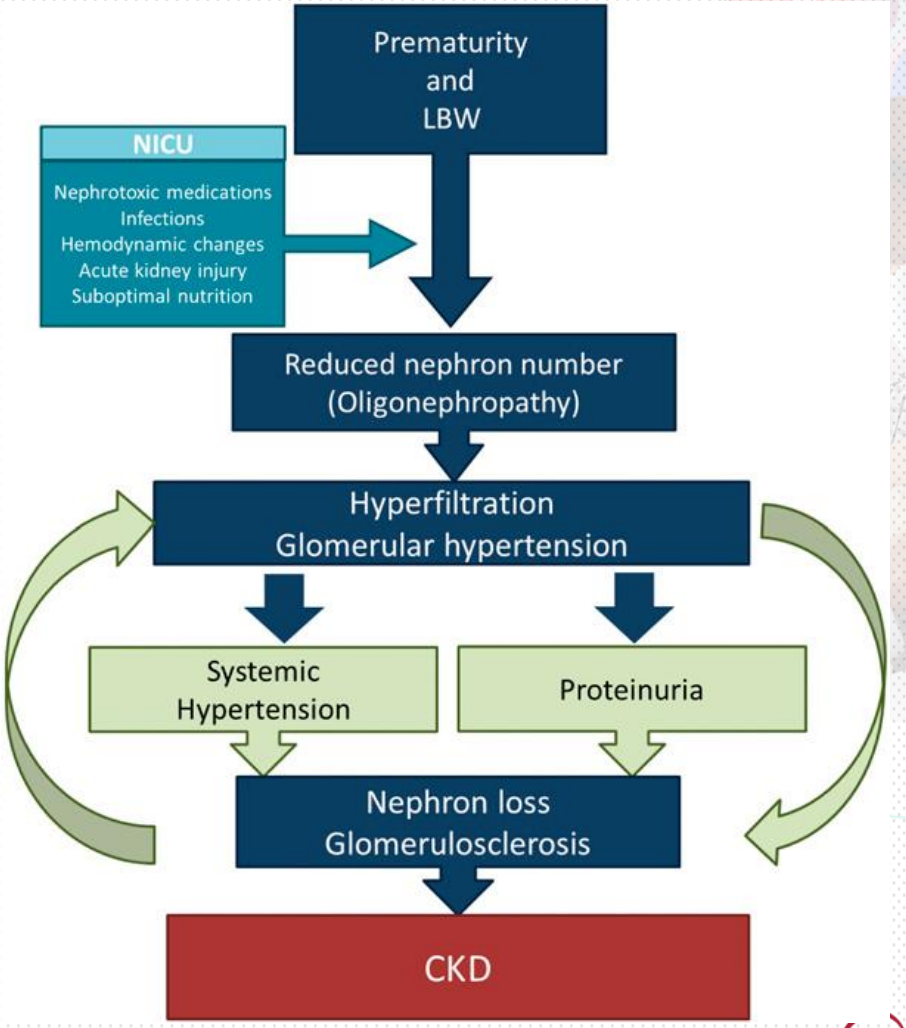
- 58 % sequellae
  - Arterial hypertension
  - Microlabuminuria
  - Impaired GFR
  - Concentrating defect
  - Hyperfiltration
- A lifelong monitoring is required

Long-term outcome of VLBW infants with neonatal AKI



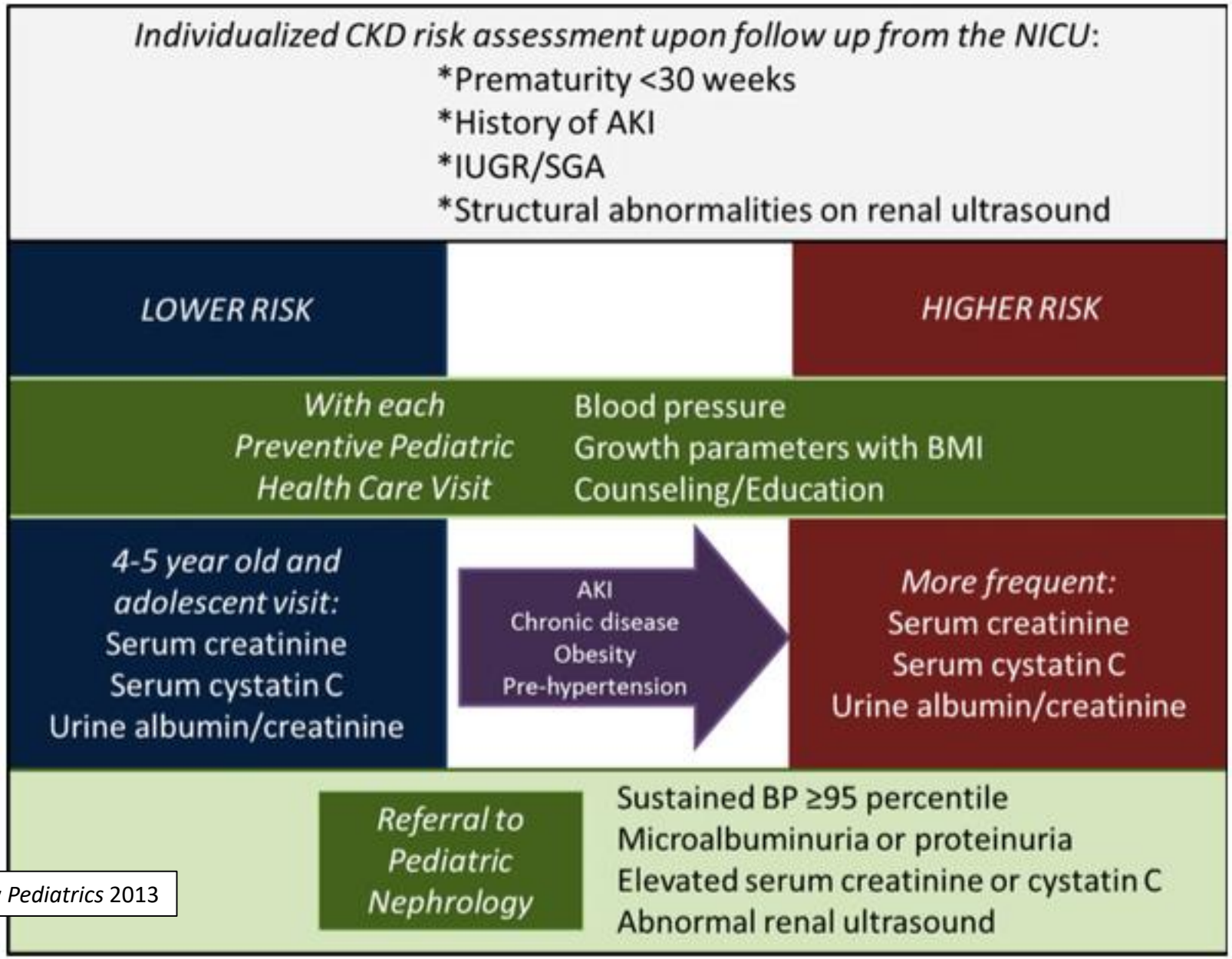
Abitbol *Pediatr Nephrol* 2003

AKI: additional risk for the developing kidney in the long term



Carmody *Pediatrics* 2013

In summary,

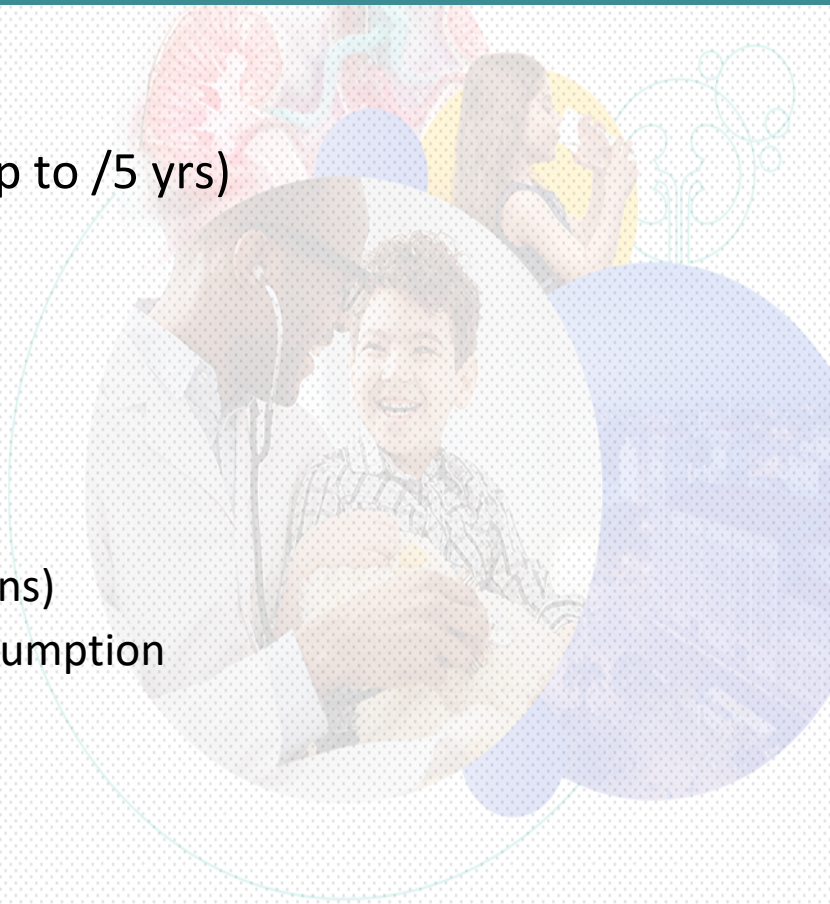


Carmody *Pediatrics* 2013

Conclusion - 1

- Anticipate at-risk conditions
- Give priority to
  - Maintenance of hemodynamics
  - Take care of any additional action
- Tricky definition
  - Looking for an ideal marker
  - Adapted investigations
- Increasing incidence (VLBW neonates)
- Prognosis
  - Extrarenal damage
  - (Very) long-term follow-up

Conclusion - 2



- Follow-up (frequency to be adapted - up to /5 yrs)
  - Serum creatinine (Schwartz)
  - Urine albumin:creatinine ratio
  - Blood pressure
- Control of risk factors
  - Normalization of diet intake (Na, proteins)
  - Prevention of obesity and tobacco consumption
  - Avoid nephrotoxicity
- Drug renoprotection?
  - ACE-i
  - ARA-2
  - Antifibrotic agents

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Thank you!