

Insufficienza renale acuta

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Terapia Intensiva Nefrologica

Azienda Ospedaliera-Universitaria Parma



AGENDA

- Epidemiology and outcome

Data and problems

- Pathogenetic mechanisms

- A new and more integrated view on AKI

- Transition from AKI to CKD

- Treatment

The need for a global approach

Acute kidney injury classification criteria								
pRIFLE Criteria ⁷			AKIN Criteria ⁹			KDIGO Criteria ¹³		
Stage	SCr-Based	Urine Output	Stage	SCr-Based	Urine Output	Stage	SCr-Based	Urine Output
Risk	>25% eCCI decrease	<0.5 mL/kg/h for 8 h	I	SCr increase ≥ 0.3 mg/dL OR 150%–200% in ≤ 48 h	<0.5 mL/kg/h for 8 h	I	SCr increase ≥ 0.3 mg/dL in 48 h OR 1.5–1.9 times	<0.5 mL/kg/h for 6–12 h
Injury	>50% eCCI decrease	<0.5 mL/kg/h for 16 h	II	SCr increase 200%–300%	<0.5 mL/kg/h for 16 h	II	SCr increase 2.0–2.9 times	<0.5 mL/kg/h for 12 h
Failure	>75% eCCI decrease OR eCCI <35 mL/min/1.73 m ²	<0.5 mL/kg/h for 24 h OR <0.3 mL/kg/h for 12 h	III	SCr increase 200%–300% OR SCr >4.0 mg/dL	<0.5 mL/kg/h for 24 h OR <0.3 mL/kg/h for 12 h	III	SCr ≥ 3.0 increase OR SCr > 4.0 mg/dL OR if <18 y of age then eCCI <35 mL/min/1.73 m ²	<0.5 mL/kg/h for 24 h OR <0.3 mL/kg/h for 12 h

Abbreviations: AKIN, Acute Kidney Injury Network; eCCI, estimated creatinine clearance; KDIGO, Kidney Disease Improving Global Outcomes; pRIFLE, pediatric version of the RIFLE criteria (Risk, Injury, Failure, and 2 outcome criteria, Loss and End-Stage Kidney Disease); SCr, serum creatinine.



Proposed neonatal acute kidney injury classification definition

Stage

0	No change or rise <0.3 mg/dl
1	↑ SCr 0.3 mg/dl or ↑ SCr 150–200% from previous trough value
2	↑ SCr 200–300% from previous trough value
3	↑ SCr 300% from previous trough value or 2.5 mg/dl or receipt of dialysis

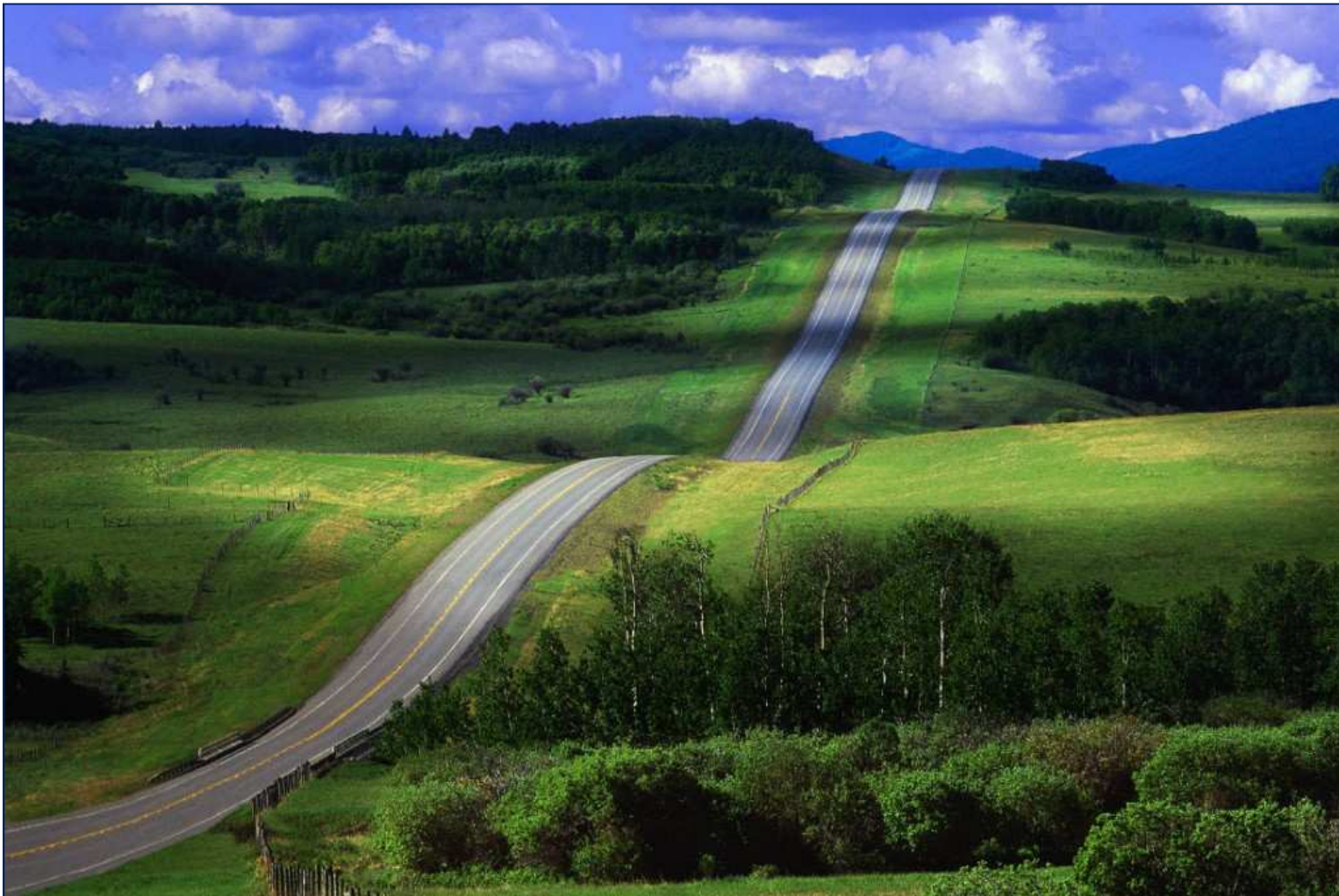
- Neonates commonly have nonoliguric AKI, making oliguria an insensitive marker
- After birth neonatal SCr reflects maternal levels



Urinary biomarkers and acute kidney injury in children: the long road to clinical application

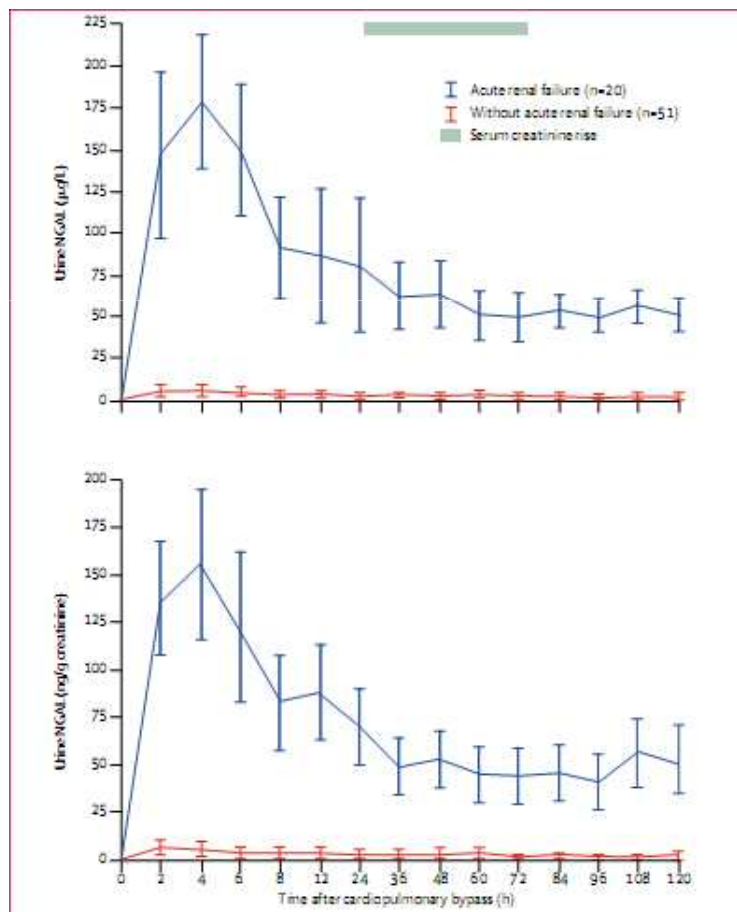
Helmut Schiffl · Susanne M. Lang

Pediatr Nephrol (2013) 28:837–842



Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery

Jaya Mishra*, Catherine Dent*, Ridwan Tarabishi*, Mark M Mitsnefes, Qing Ma, Caitlin Kelly, Stacey M Ruff, Kamyar Zahedi, Mingyuan Shao, Judy Bean, Kiyoshi Mori, Jonathan Barasch, Prasad Devarajan



ROC area 0.998 2-hr urine NGAL
ROC area 0.91 2-hr serum NGAL



Lancet 2005; 365: 1231-38

Performance of Kidney Injury Molecule-1 and Liver Fatty Acid-Binding Protein and Combined Biomarkers of AKI after Cardiac Surgery

Table 7. Biomarker combinations in children

Biomarker Combination	Day 1		Day 2
	0–6 h	6–12 h	
Individual biomarkers			
Urine KIM-1 (ng/ml)	0.64 (0.04)	0.64 (0.04)	0.63 (0.05)
Urine L-FABP (ng/ml)	0.70 (0.04)	0.71 (0.04)	0.66 (0.05)
Urine IL-18 (pg/ml) (8)	0.72 (0.04)	0.76 (0.04)	0.60 (0.05)
Urine NGAL (ng/ml) (8)	0.71 (0.04)	0.69 (0.04)	0.59 (0.05)
Plasma NGAL (ng/ml) (8)	0.56 (0.05)	NA	0.57 (0.05)
Best combinations across time points			
Two-way combinations			
Urine IL-18 day 1 (0–6 h) and urine L-FABP day 2		0.78 (0.04)	
3-way combinations			
Urine IL-18 day 1 (0–6 h), urine NGAL day 1 (0–6 h), and urine L-FABP day 2		0.78 (0.04)	



AKI in Hospitalized Children: Epidemiology and Clinical Associations in a National Cohort

Scott M. Sutherland, Jun Ji,[†] Farnoosh H. Sheikhi,[‡] Eric Widen,[‡] Lu Tian,[§] Steven R. Alexander,* and Xuefeng B. Ling[†]*

- Of 2,644,263 children, 10,322 children developed AKI (3.9/1000 admissions);
- In-hospital mortality among patients with AKI was 15.3%, but higher among children <1 month old (31.3% versus 10.1%, P,0.001) and children requiring critical care (32.8% versus 9.4%, P 0.001) or dialysis (27.1% versus 14.2%, P 0.001);
- Shock, septicemia, intubation/mechanical ventilation, circulatory disease, cardiac congenital anomalies, and extracorporeal support were significantly associated with AKI



World Incidence of AKI: A Meta-Analysis

Paweena Susantitaphong,^{*†‡} Dinna N. Cruz,[§] Jorge Cerda,^{||} Maher Abulfaraj,^{*} Fahad Alqahtani,^{*} Ioannis Koulouridis,^{*†} and Bertrand L. Jaber,^{*†} for the Acute Kidney Injury Advisory Group of the American Society of Nephrology

Pooled incidence rate of AKI according to the KDIGO-equivalent definition

Subgroup	Studies (n)	Patients (n)	Patients with AKI (n)	AKI Incidence Rate (%)	95% Confidence Interval	Test for Heterogeneity	
						I ² Index	Q Test P Value
All	154	3,585,911	573,424	23.2	21.0 to 25.7	99.9	<0.001
Age category							
Adults	130	2,571,691	569,861	21.6	19.2 to 24.1	99.9	<0.001
Children	24	14,220	3563	33.7	26.9 to 41.3	98.3	<0.001
Clinical setting							
Community acquired	7	548,398	4897	8.3	1.6 to 33.0	99.9	<0.001
Critical care	41	888,604	272,580	31.7	28.6 to 35.0	99.9	<0.001
Cardiac surgery	42	164,333	33,157	24.3	20.4 to 28.8	99.7	<0.001
Trauma	4	14,947	2557	19.9	13.6 to 28.2	98.7	<0.001
Heart failure	1	682	221	32.4	29.0 to 36.0	—	—
Hematology/oncology	3	2401	453	21.3	7.5 to 47.6	99.2	<0.001
Nephrotoxins	4	17,786	1681	12.2	6.2 to 22.7	98.7	<0.001
Hospital acquired, unspecified	52	1,948,760	257,878	20.9	17.2 to 25.2	99.9	<0.001



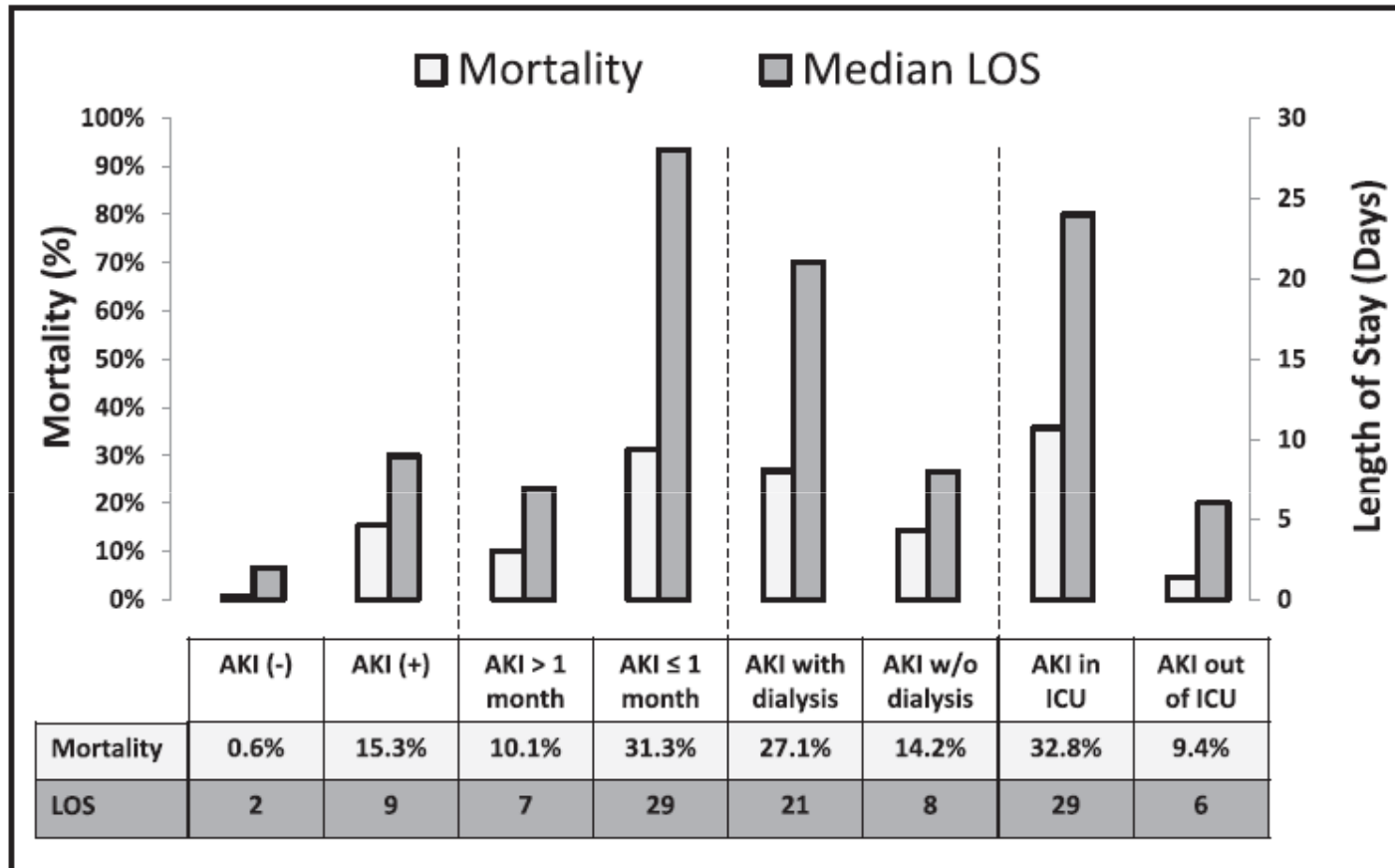
Clin J Am Soc Nephrol 8: 1482–1493, 2013.

Shift in pAKI epidemiology

Author	Time span	Cohort	AKI cause
Williams et al. [8], 2002	1978–1998	all hospital	1978–88: HUS 38%, oncology 8% 1988–98: HUS 22%, oncology 17%
Hui-Stickle et al. [4], 2005	1999–2001	all hospital	ischemic 21% nephrotoxins 16% primary renal 7%
Akcan-Arikan et al. [20], 2007	2005–2006	pediatric intensive care unit	pneumonia 33% SIRS/sepsis 27% cardiogenic 10%
Ball and Kara [10], 2008	2001–2006	pediatric intensive care unit receiving RRT	cardiogenic 58% HUS 17% sepsis 13%



Mortality and LOS associated with AKI



Mortality rates and length of stay are shown for patients with and without AKI, AKI patients < 1 and > 1 month of age, AKI patients who required and did not require dialysis, and AKI patients who received and did not receive critical care.

Acute kidney injury is an independent risk factor for pediatric intensive care unit mortality, longer length of stay and prolonged mechanical ventilation in critically ill children: a two-center retrospective cohort study

Omar Alkandari^{1†}, K Allen Eddington^{2†}, Ayaz Hyder¹, France Gauvin², Thierry Ducruet³, Ronald Gottesman⁴, Véronique Phan⁵ and Michael Zappitelli^{1*}

- Mortality risk increased by 3 to 6 times
- Length-of Hospital Stay increased
- 20% of patients leave the PICU with higher than basal serum creatinine levels

Alkandari et al. *Critical Care* 2011, **15**:R146



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Differential diagnosis of pediatric acute kidney disease

Prerenal azotemia	Intrinsic AKI		Obstructive AKI
<p>Loss of effective blood volume</p> <p>Absolute loss</p> <ul style="list-style-type: none"> Hemorrhage Gastrointestinal losses Renal losses Skin losses <p>Relative loss: capillary leak</p> <ul style="list-style-type: none"> Sepsis Hypoalbuminemia <p>Extracorporeal membrane oxygenation</p> <p>Heart failure</p> <p>Pharmacologic agents</p> <ul style="list-style-type: none"> Indomethacin Tolazoline ACE inhibitors ARB 	<p>Renal artery damage</p> <p>Renal vein damage</p> <p>Acute tubular necrosis</p> <ul style="list-style-type: none"> Severe renal ischemia Nephrotoxins Aminoglycosides Indomethacin Amphotericin B Calcineurin inhibitors Radiocontrast dyes Myoglobinuria Hemoglobinuria Heavy metals/poison <p>Intra-renal obstruction</p> <ul style="list-style-type: none"> Acyclovir Uric acid <p>Infections</p> <ul style="list-style-type: none"> Pyelonephritis <p>Radiation/chemotherapy</p>	<p>Interstitial nephritis</p> <ul style="list-style-type: none"> Drugs Virus/bacteria Infiltration Lymphoma Sarcoid <p>Glomerular causes</p> <ul style="list-style-type: none"> Postinfections IgA nephropathy Membranoproliferative Lupus ANCA Ab-associated Pauciimmune GN Goodpasture's disease anti-GBM Microangiopathies <p>Renal vascular causes</p> <ul style="list-style-type: none"> Renal artery thrombosis Renal vein thrombosis 	<p>Congenital malformations</p> <ul style="list-style-type: none"> Imperforate prepuce Urethral stricture PUV Urethral diverticulum Ureterocele Megaureter UPJ obstruction <p>Extrinsic compression</p> <ul style="list-style-type: none"> Intrinsic obstruction Renal calculi Fungus balls Neurogenic bladder



Acute Kidney Injury and Increasing Nephrotoxic-Medication Exposure in Noncritically-Ill Children

Brady S. Moffett* and Stuart L. Goldstein†

Clin J Am Soc Nephrol 6: 856–863, 2011.

Acute kidney injury in non-critically ill children treated with aminoglycoside antibiotics in a tertiary healthcare centre: a retrospective cohort study

Nephrol Dial Transplant (2011) 26: 144–150

Michael Zappitelli¹, Brady S. Moffett², Ayaz Hyder³ and Stuart L. Goldstein⁴

Nonsteroidal Anti-Inflammatory Drugs Are an Important Cause of Acute Kidney Injury in Children

Jason M. Misurac, MD¹, Chad A. Knoderer, PharmD², Jeffrey D. Leiser, MD, PhD¹, Corina Năilescu, MD¹, Amy C. Wilson, MD¹, and Sharon P. Andreoli, MD¹

J Pediatr 2013;162:1153-9,



Onco-Nephrology: Tumor Lysis Syndrome

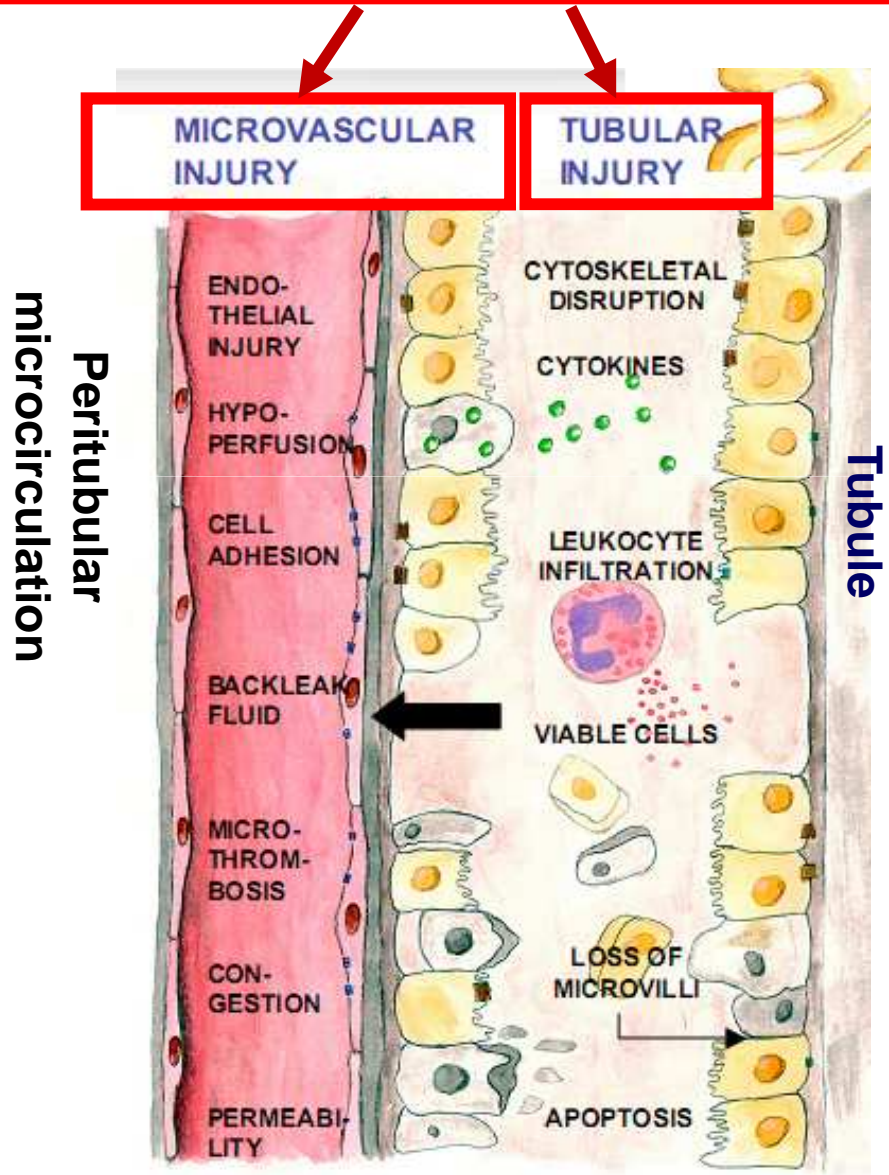
F. Perry Wilson and Jeffrey S. Berns

Table 2. Incidence of tumor lysis syndrome in various malignancies

Malignancy (Reference)	Incidence (%)	Risk
Hematologic		
Burkitt lymphoma (33)	14.9	High
B cell ALL (33)	26.4	High
diffuse large-B cell lymphoma (87)	6	Intermediate
ALL	5.2–23	May vary by WBC count, with >100,000 cells/mm ³ being highest risk
AML: WBC count >75,000 cells/mm ³ (37)	18	High
AML: WBC count 25,000–75,000 cells/mm ³ (37)	6	Intermediate
AML: WBC count <25,000 cells/mm ³ (37)	1	Low
chronic lymphocytic leukemia (88)	0.33	Low (higher with WBC >100,000 cells/mm ³)
chronic myeloid leukemia (89)	Case reports only	Low
multiple myeloma (90)	1	Low
Nonhematologic		
solid tumors (35)	Unknown	Low



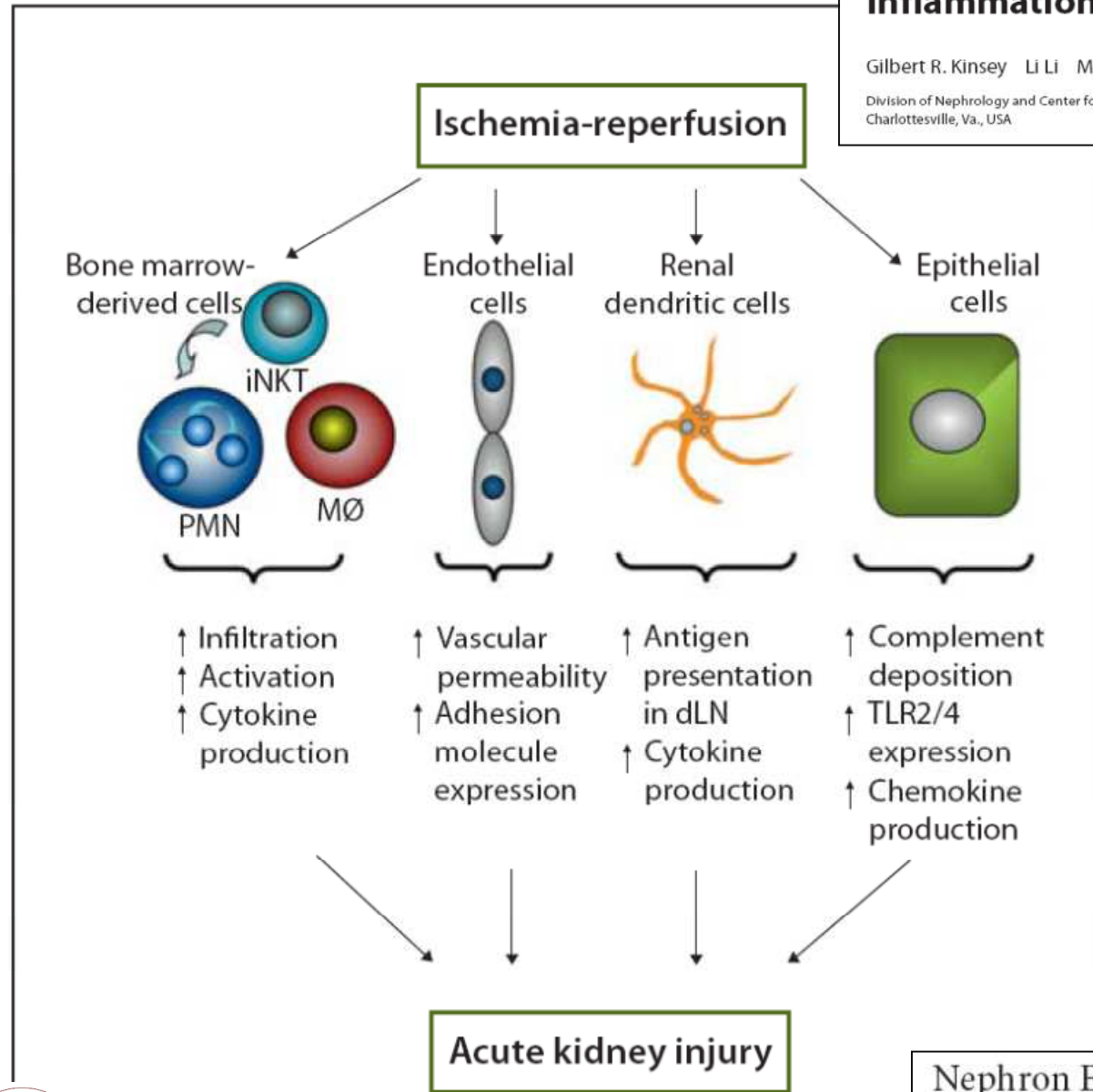
Renal hypoperfusion/ ischemia ± direct nephrotoxicity



Inflammation in Acute Kidney Injury

Gilbert R. Kinsey Li Li Mark D. Okusa

Division of Nephrology and Center for Immunity, Inflammation and Regenerative Medicine, University of Virginia, Charlottesville, Va., USA

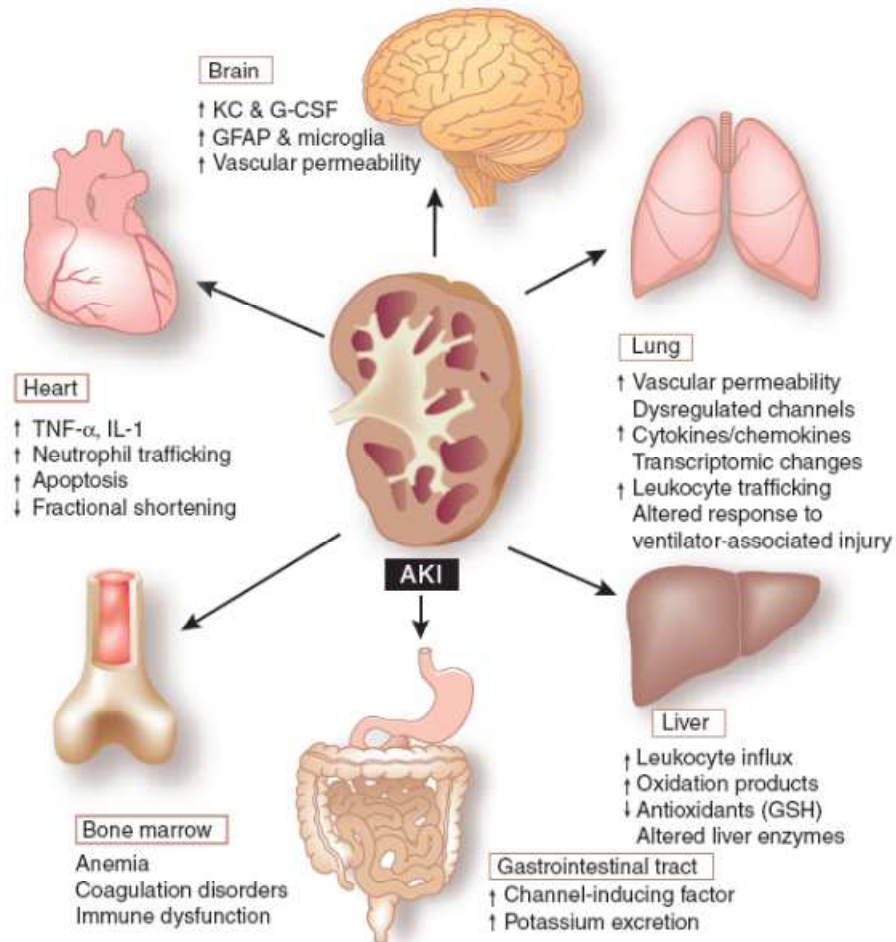


AKI as an immune-inflammatory syndrome activated by ischemia-reperfusion injury

Nephron Exp Nephrol 2008;109:e102-e107



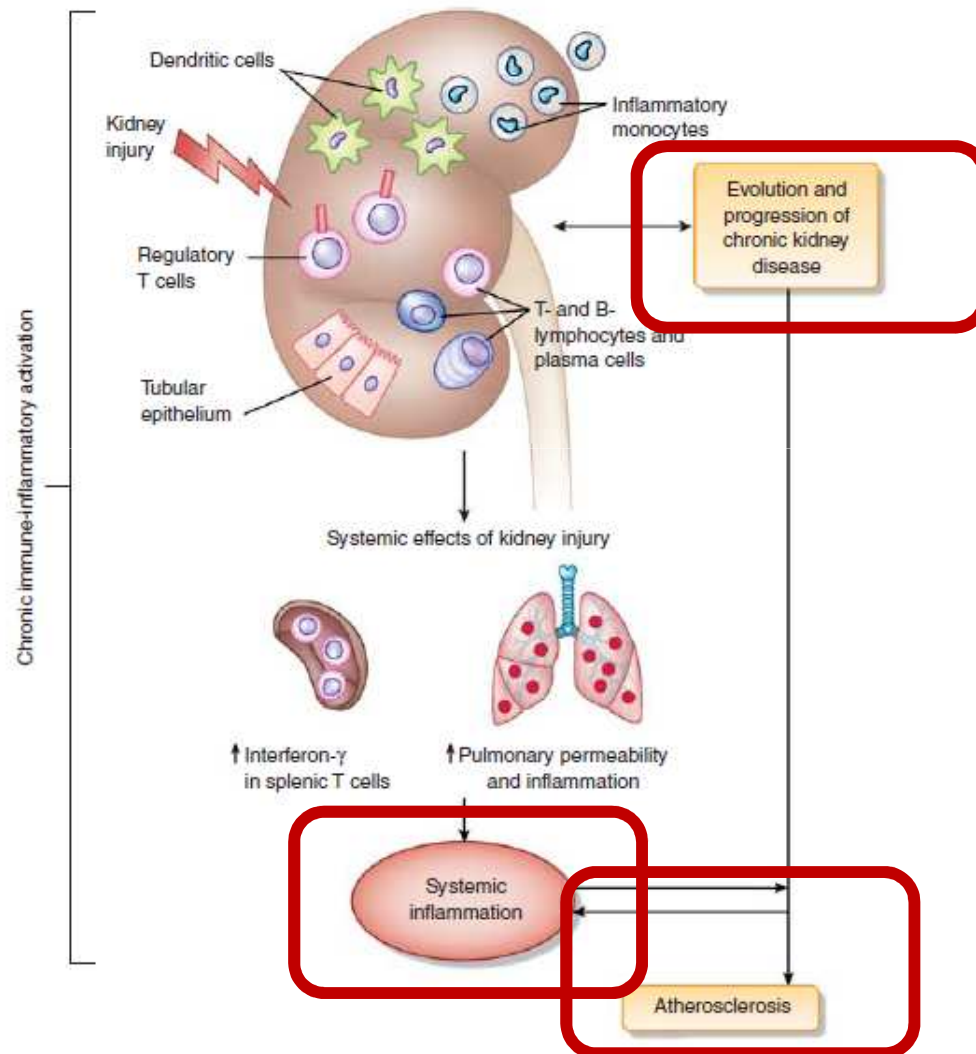
AKI-induced distant organ effects: The systemic complications of AKI as the consequence of a “nephro-centric” inflammatory syndrome



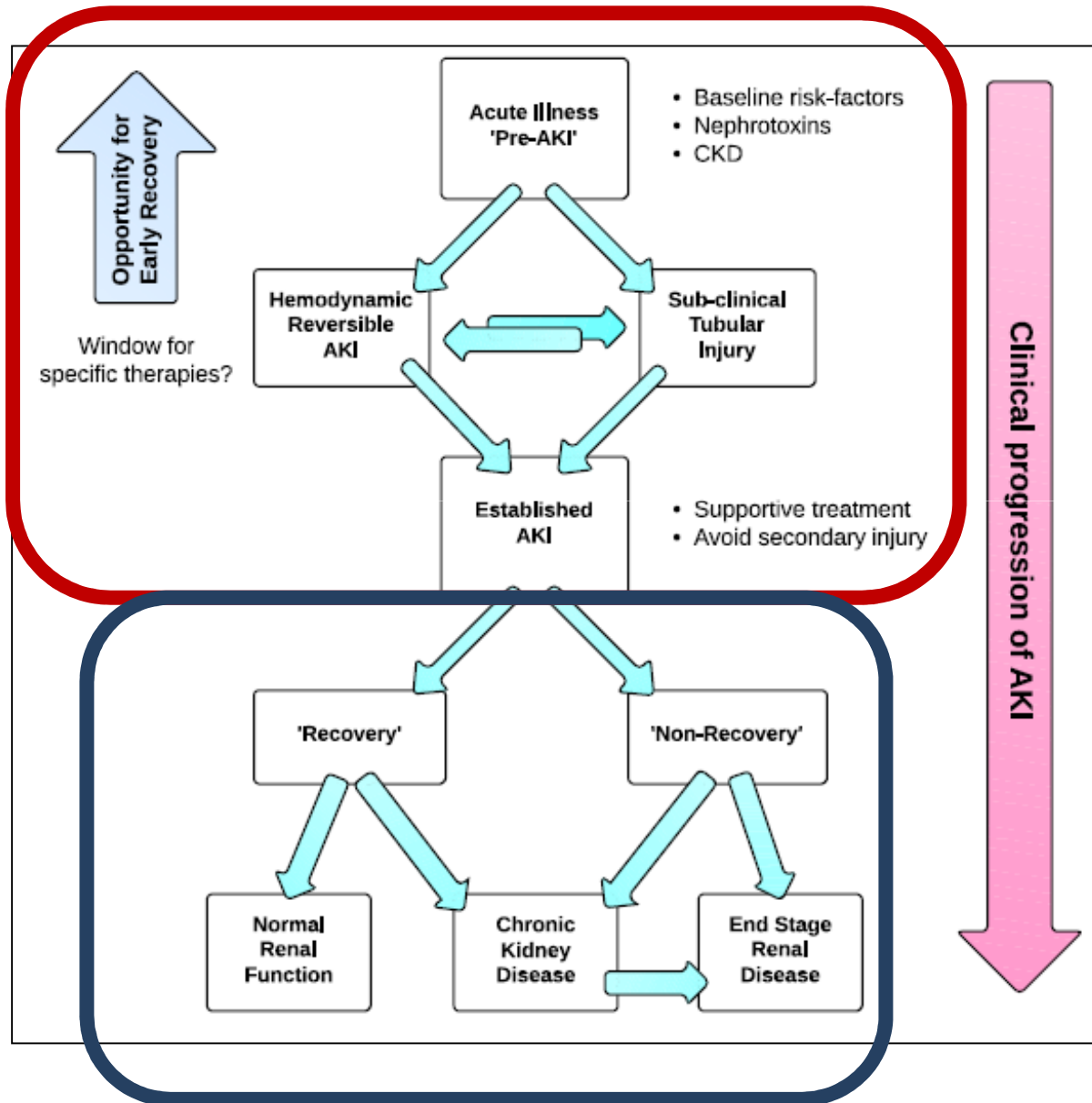
Scheel PJ et al, Kidney Int 2008; 74:849-851



Novel inflammatory mechanisms of accelerated atherosclerosis in kidney disease



Clinical course of AKI



Nephrogenesis: key data

- Nephrogenesis in human begins around 6-week gestation age, and is normally completed by 36 week gestation
- No evidence of active postnatal glomerulogenesis in at term babies
- The number of nephrons formed within the kidney at completion of nephrogenesis influences lifetime renal functional capacity and reserve → it is essential that adequate nephrogenesis is achieved at the very beginning of life



Accelerated Maturation and Abnormal Morphology in the Preterm Neonatal Kidney

Megan R. Sutherland,* Lina Gubhaju,* Lynette Moore,[†] Alison L. Kent,[‡] Jane E. Dahlstrom,[§] Rosemary S. C. Horne,^{||} Wendy E. Hoy,[¶] John F. Bertram,* and M. Jane Black*

- In the kidneys of preterm neonates renal maturation accelerated after preterm birth, with a decreased width of the nephrogenic zone
- Compared with gestational controls, preterm kidneys had a greater percentage of morphologically abnormal glomeruli and a significantly larger cross-sectional area of the renal corpuscle, suggestive of renal hyperfiltration
- These observations suggest that the preterm kidney may have fewer functional nephrons, thereby increasing vulnerability to impaired renal function in both the early postnatal period and later in life.



Nephrol Dial Transplant (2013) 28: 1325–1328
doi: 10.1093/ndt/gfs538
Advance Access publication 11 December 2012



In Focus

The nephron number counts—from womb to tomb

Maarten B. Rookmaaker
and Jaap A. Joles

Department of Nephrology and Hypertension, University Medical
Center Utrecht, Utrecht 3584 CX, the Netherlands

Is Low Birth Weight an Antecedent of CKD in Later Life? A Systematic Review of Observational Studies

*Sarah L. White, MPH,¹ Vlado Perkovic, FRACP, PhD,¹ Alan Cass, FRACP, PhD,¹
Choon Lan Chang, PhD,² Neil R. Poulter, FRCP, MSc, PhD,² Tim Spector, FRCP, MD,³
Leigh Haysom, FRACP, PhD,⁴ Jonathan C. Craig, FRACP, PhD,^{4,5} Isa Al Salmi, FRACP, MD,⁶
Steven J. Chadban, FRACP, PhD,⁷ and Rachel R. Huxley, DPhil¹*

- 32 studies (46,249 patients), low birth weight defined as birth weight between 1,500 and 2,500 g
- **LBW associated with a 70% increase of risk of developing CKD later in life (HR: 1.73, 95% CI: 1.44–2.08) and with an 80% greater risk of developing albuminuria (HR: 1.81, 95% CI: 1.19–2.77) compared to normal birth weight infants**



**Long-term Risk of CKD in Children Surviving Episodes of Acute
Kidney Injury in the Intensive Care Unit: A Prospective
Cohort Study**

*Cherry Mammen, MD, MHSc¹, Abdullah Al Abbas, MD,¹ Peter Skippen, MD,²
Helen Nadel, MD,³ Daniel Levine, MD,³ J.P. Collet, MD, PhD,⁴ and
Douglas G. Matsell, MD¹*

- CKD incidence at 1-3 yrs 10.3% (17.1%
in patients with AKIN stage 3)
- 46.8% of patients at risk for CKD
(hypertension, eGFR 60-90 ml/min/1.73
m², proteinuria) and/or hyperfiltration



Uremic memory: the role of acute kidney injury in long-term outcomes

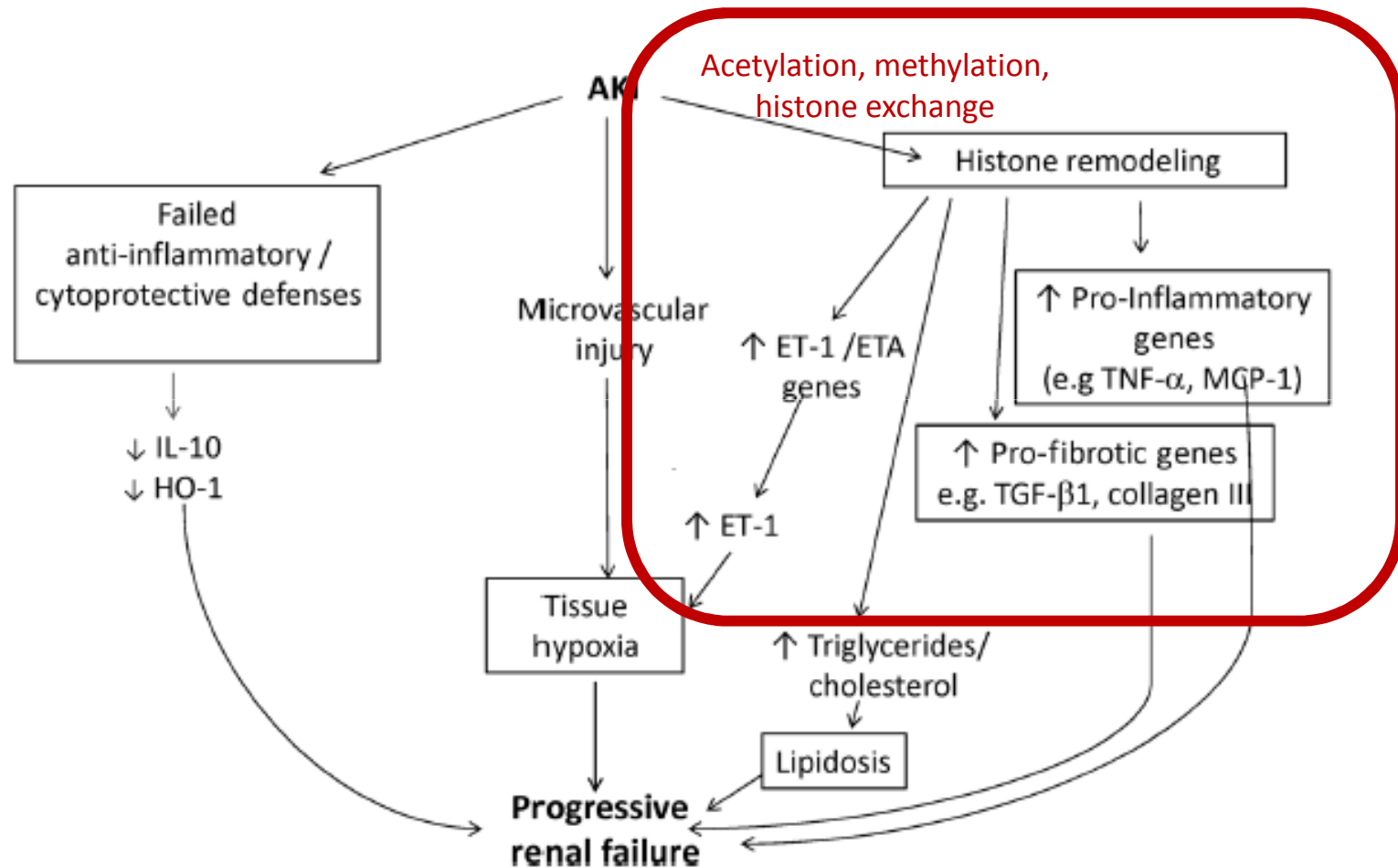
Ladan Golestaneh¹, Michal L. Melamed¹ and Thomas H. Hostetter¹

Most epidemiologic data, thus far, have focused on short-term outcomes of acute kidney injury (AKI). Lo *et al.* correlate AKI with long-term outcomes. The concept of 'uremic memory' sheds light on the importance of AKI and its permanent imprint. The focus of research should be on prevention of an episode of AKI, when possible.

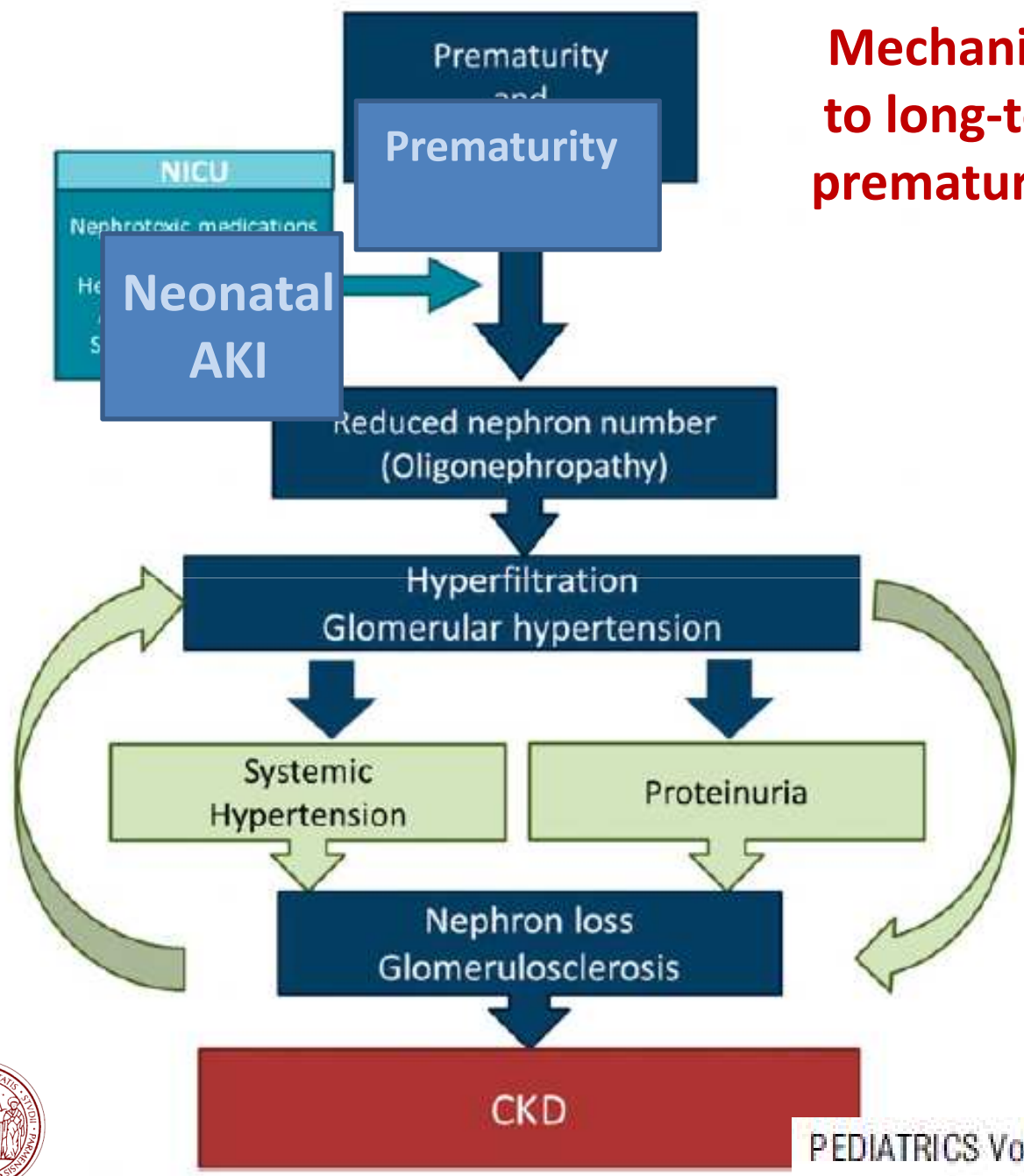
Kidney International (2009) 76, 813–814. doi:10.1038/ki.2009.314



Potential pathways by which ischemic AKI may initiate progressive renal disease



Mechanisms of vulnerability to long-term renal disease in prematurity and neonatal AKI



According to Brenner's hypothesis, reduced nephron number (oligonephropathy) leads to hyperfiltration, hypertension, and proteinuria, which perpetuate renal damage and lead to glomerulosclerosis and CKD



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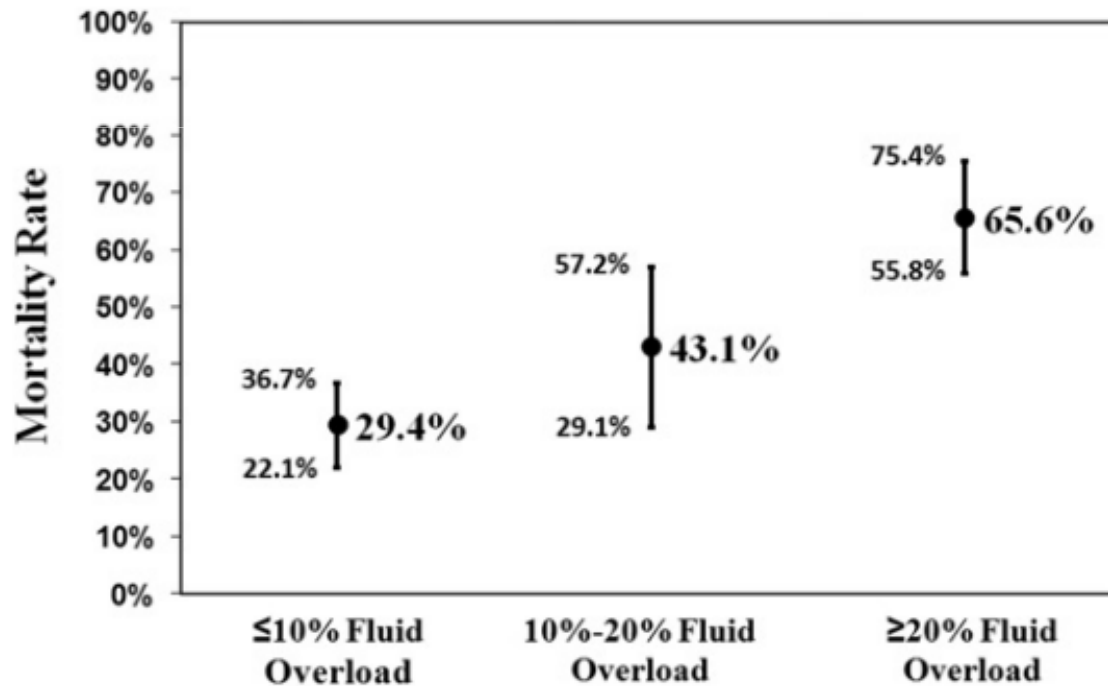
Treatment of pediatric AKI

- Specific therapy of the causal factor (for example antibiotics, surgery etc.)
- General supportive therapy (fluids, vasoactive agents, mechanical ventilation etc.)
- Renal replacement therapy
- Nutritional supplementation



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

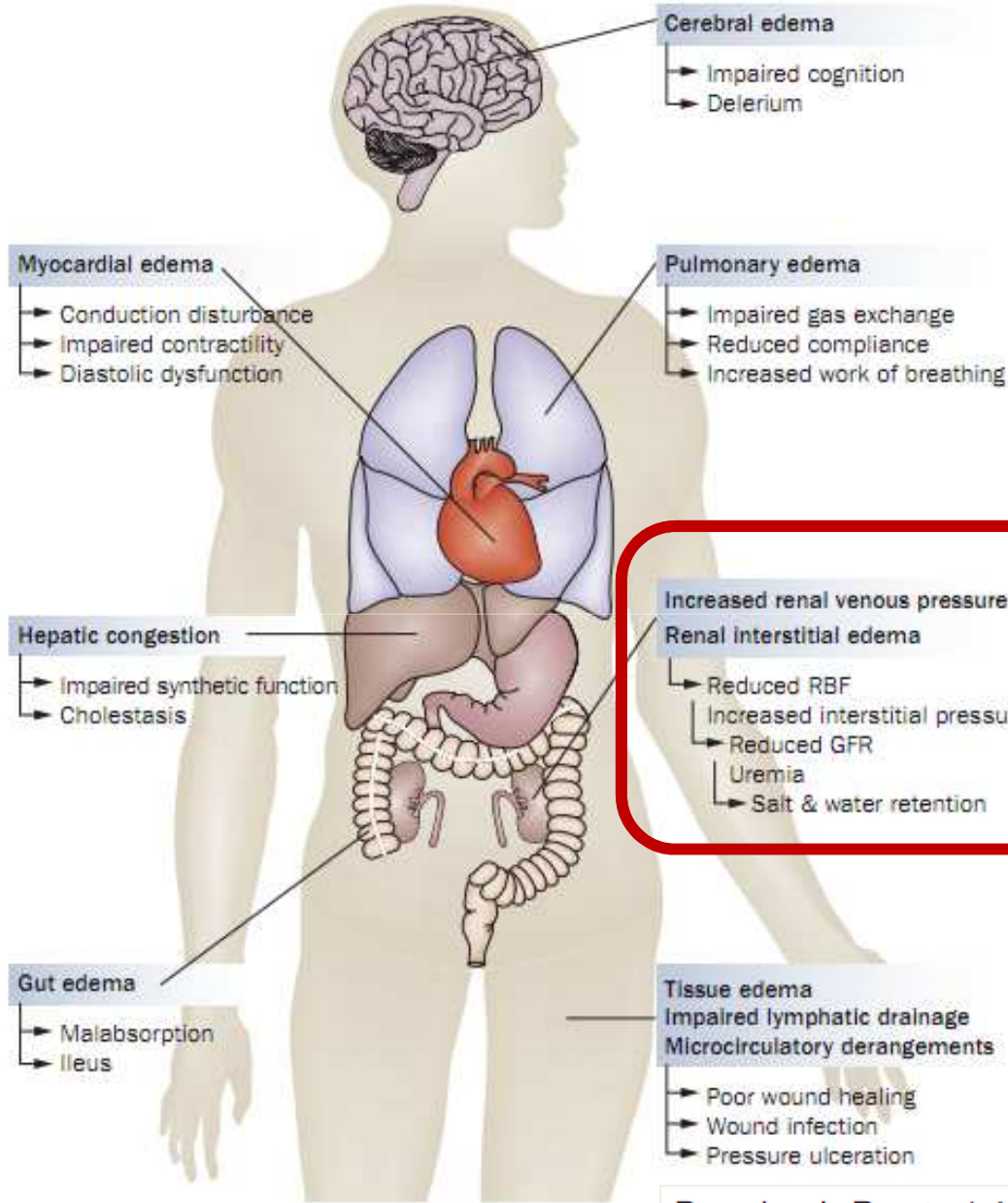
Scott M. Sutherland, MD,¹ Michael Zappitelli, MD, MSc,² Steven R. Alexander, MD,¹
Annabelle N. Chua, MD,³ Patrick D. Brophy, MD,⁴ Timothy E. Bunchman, MD,⁵
Richard Hackbarth, MD,⁵ Michael J.G. Somers, MD,⁶ Michelle Baum, MD,⁶
Jordan M. Symons, MD,⁷ Francisco X. Flores, MD,⁸ Mark Benfield, MD,⁹ David 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, MD³



Mortality in
AKI is
increased
when FO
increases



Why mortality is increased with FO?

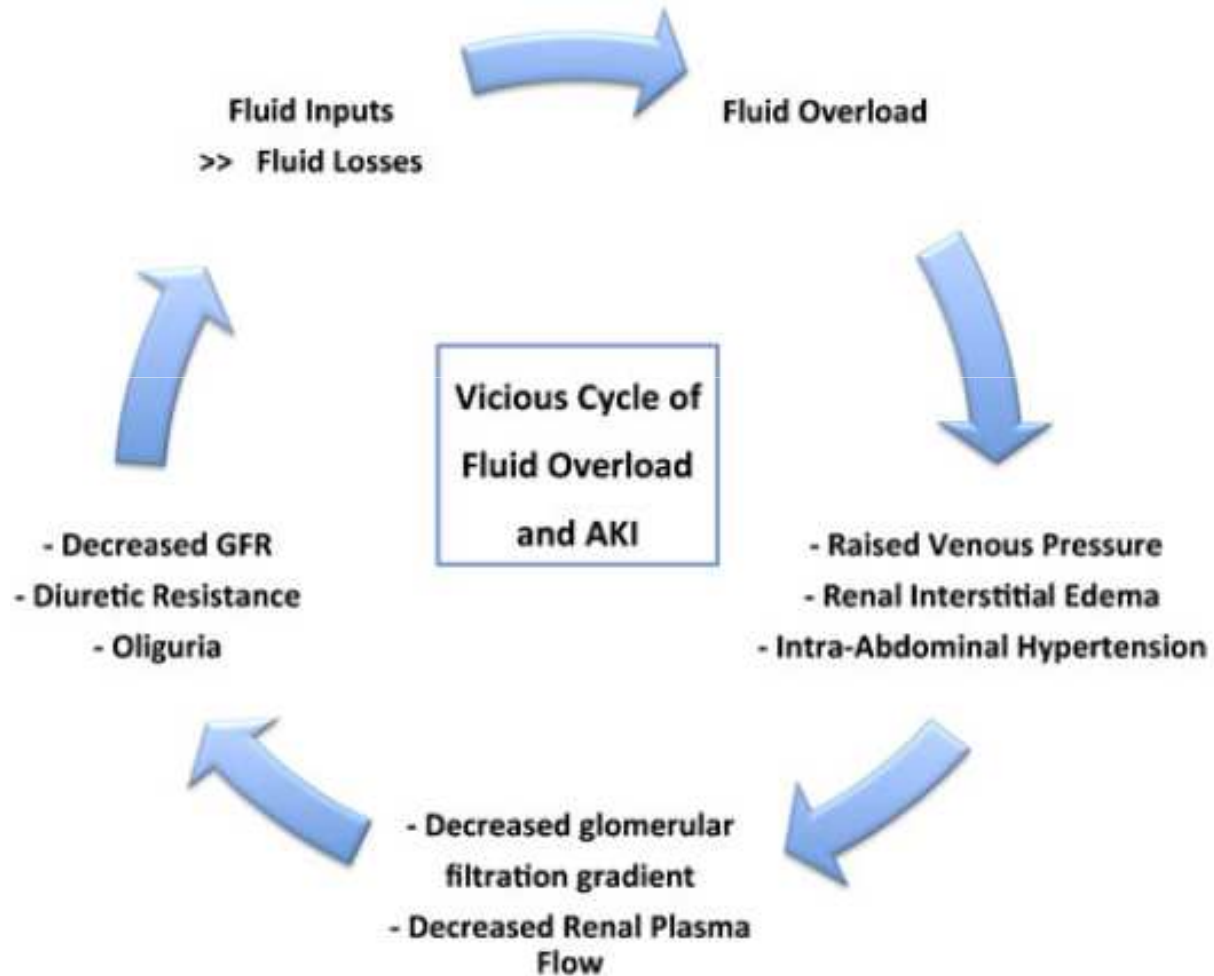


No single organ system is spared by the pathological sequelae of fluid overload (congestion)

Prowle, J. R. et al. *Nat. Rev. Nephrol.* 6, 107–115 (2010)



Inter-relationship between fluid overload and AKI: FO may worsen AKI, and AKI may contribute to FO



Renal replacement therapy

- Timing
- Dose
- Modality
- Anticoagulation



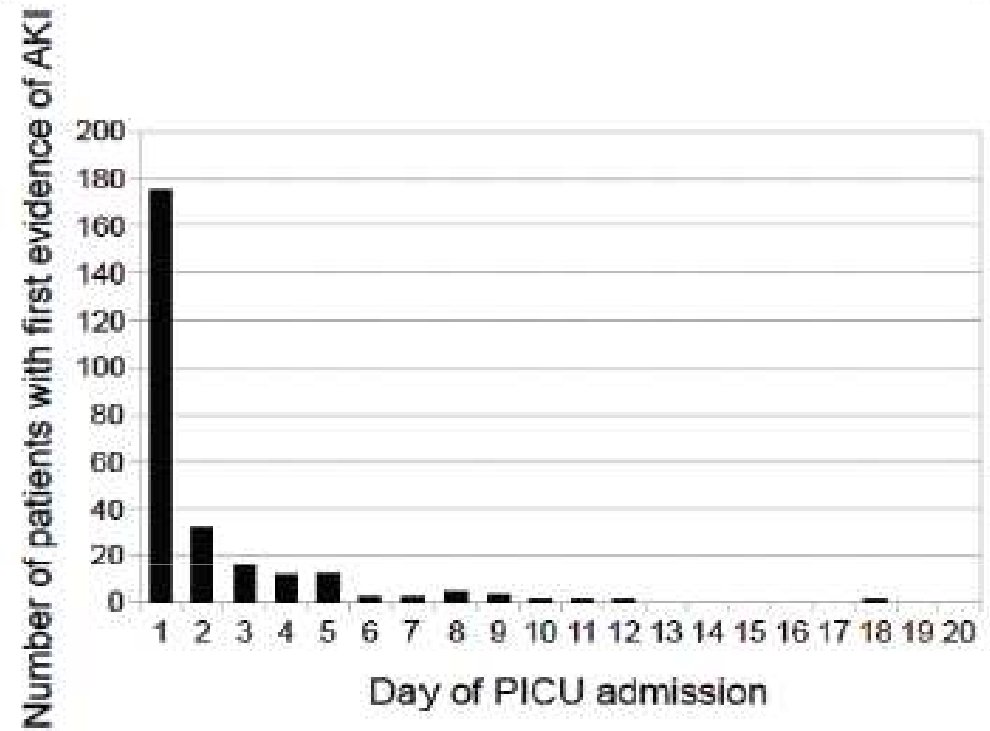


Figure 3 Day of PICU admission when AKI first occurred at the Montreal Children's Hospital center. Histograms of patients with acute kidney injury (AKI) depicting the number of patients who first developed AKI on each day of pediatric intensive care unit (PICU) admission. Data are representative of only the Montreal Children's Hospital center.

Alkandari et al. *Critical Care* 2011, **15**:R146



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 Bojan¹, Simone Gioanni¹, Pascal R. Vouhé^{2,3}, Didier Journois^{3,4} and Philippe Pouard¹

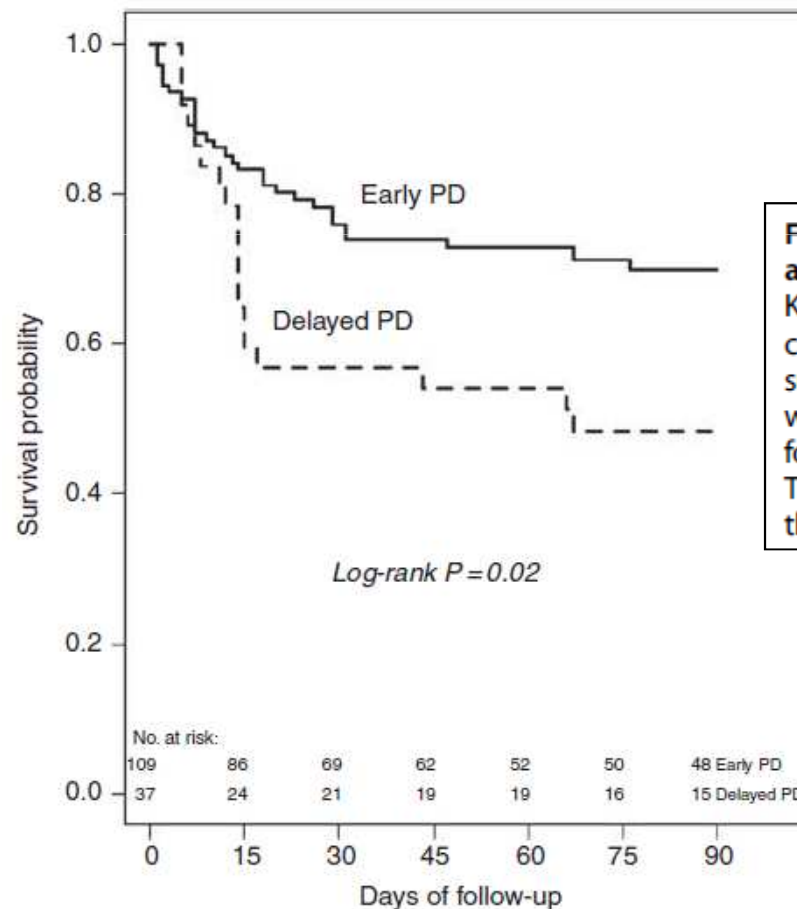


Figure 2 | Ninety-day survival among patients with early and delayed peritoneal dialysis. Survival is shown using Kaplan-Meier curves. Patients with peritoneal dialysis (PD) commenced on the day of surgery or on the day following surgery ('Early PD' group) had a better 90-day survival compared with patients in whom PD was commenced on the second day following surgery or later ('Delayed PD' group), 72.5% vs. 48.7%. The *P*-value refers to the between group difference assessed by the result of the log-rank test = 5.7, with 1 degree of freedom.



Indications to RRT start in pediatric AKI

- 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) that are refractory to medical management

UpToDate 2013



RRT modalities

- Peritoneal dialysis
- Intermittent dialysis
- CRRT



Treatment of critically ill children with kidney injury by sustained low-efficiency daily diafiltration

Chia-Ying Lee • Huang-Chieh Yeh • Ching-Yuang Lin

SLEDD-f provides good hemodynamic tolerance and correction of fluid overload, pH, and electrolyte imbalance for critically ill children with AKI.

Pediatr Nephrol (2012) 27:2301–2309



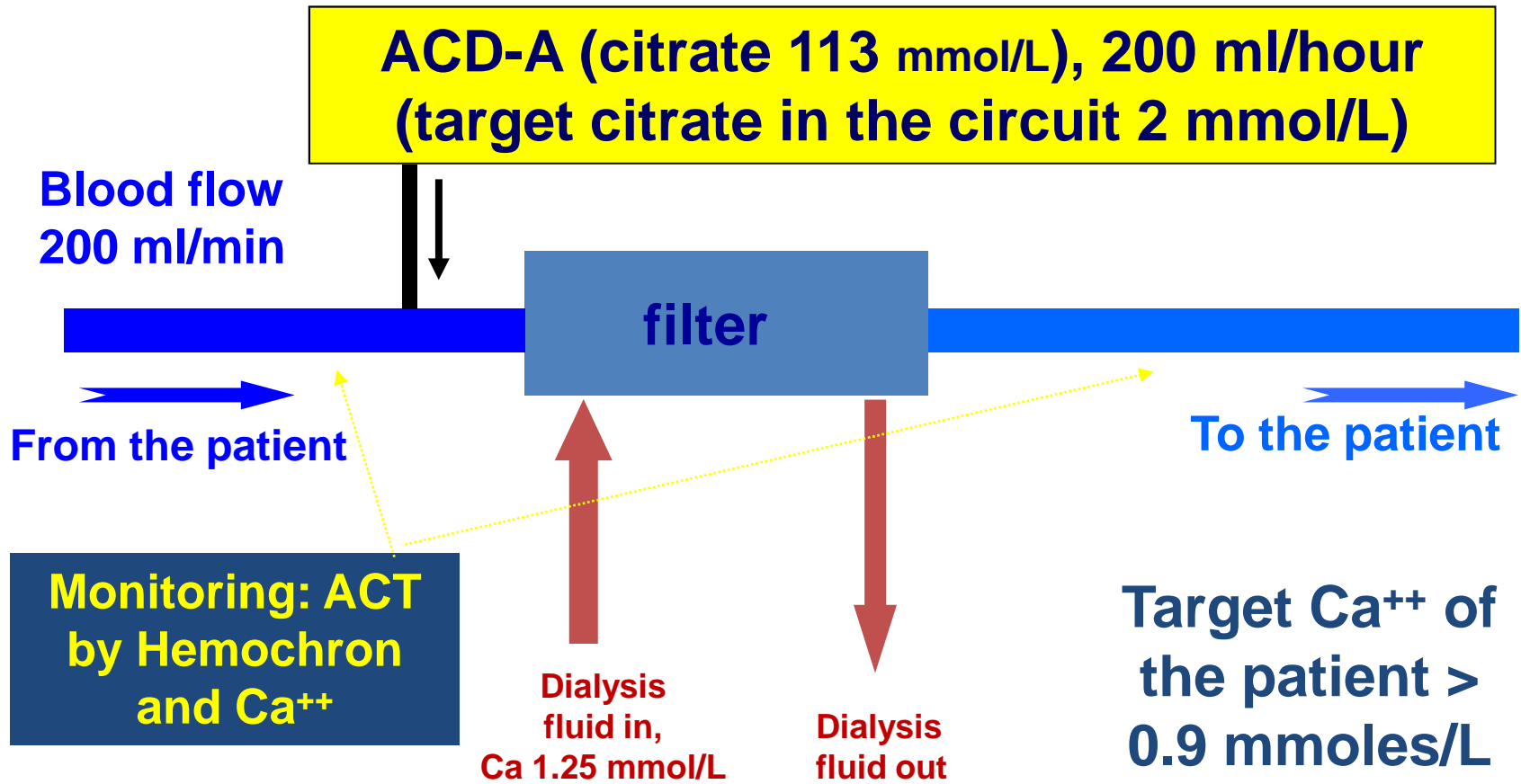
Efficacy and Safety of a Citrate-Based Protocol for Sustained Low-Efficiency Dialysis in AKI Using Standard Dialysis Equipment

Enrico Fiaccadori, Giuseppe Regolisti,* Carola Cademartiri,* Aderville Cabassi,* Edoardo Picetti,[†] Maria Barbagallo,[‡] Tiziano Gherli,[§] Giuseppe Castellano,^{||} Santo Morabito,[¶] and Umberto Maggiore***

Clin J Am Soc Nephrol 8: 1670–1678, 2013.



Sustained, low-efficiency dialysis (SLED) with ACD-A



- Dialysis fluid rate 300 ml/min
- Daily treatments, 8 to 12 hours
- Standard dialysis machine
- polysulfone filters, 1.7 m², KUF 20 ml/mmHg/h



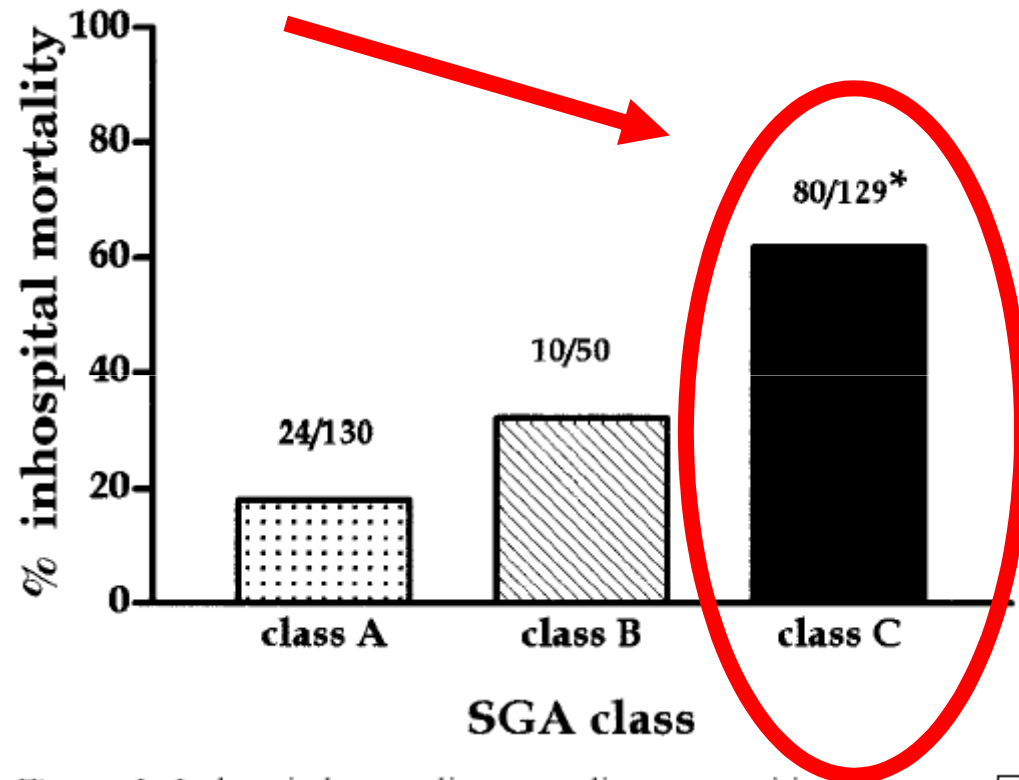
Nutrition as Medical Therapy in Pediatric Critical Illness

Timothy E. Bunchman

Clin J Am Soc Nephrol 8: 513–514, 2013. doi: 10.2215/CJN.01800213



Protein-energy wasting is associated with increased mortality risk in AKI



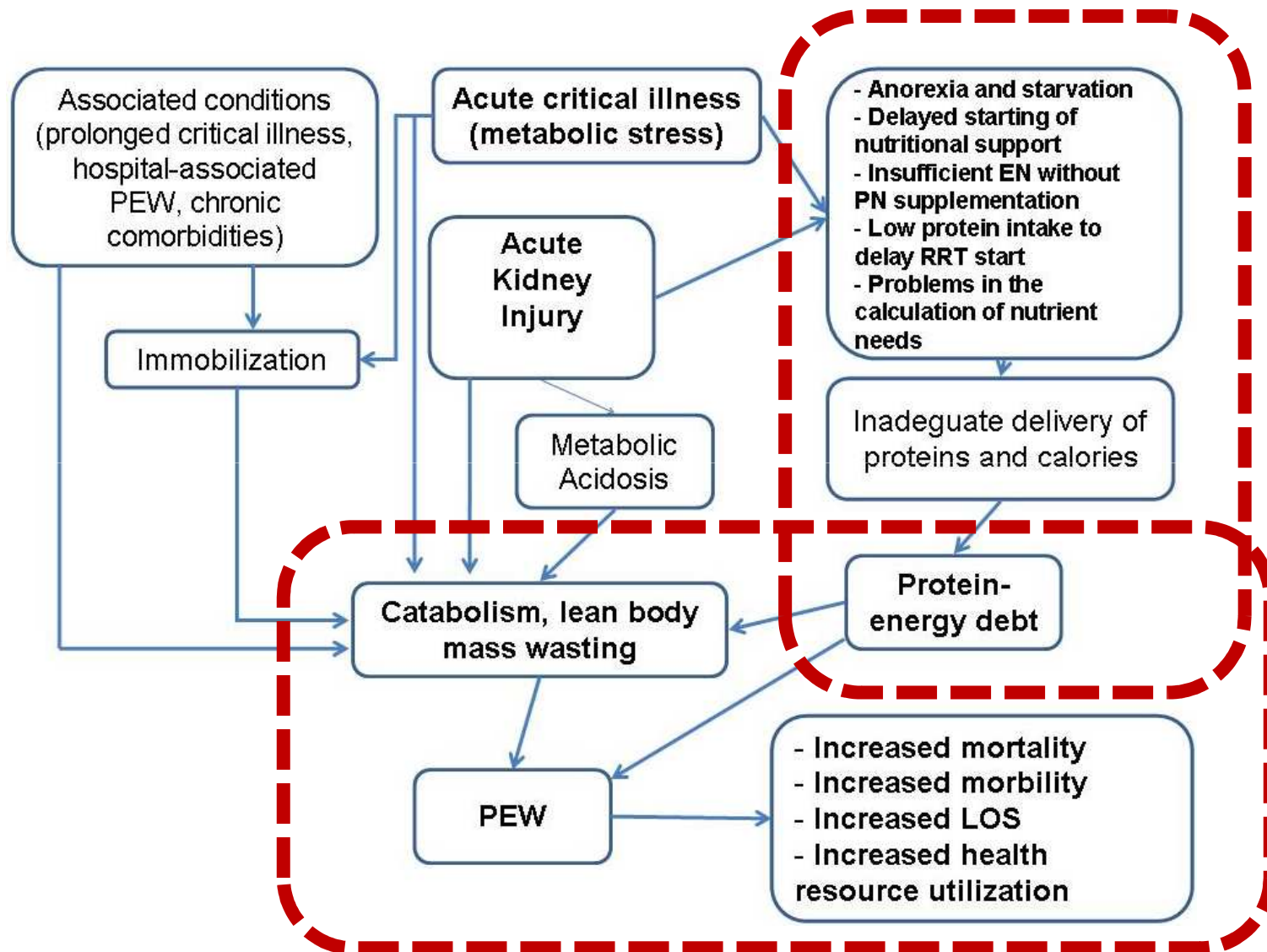
In-hospital mortality according to nutritional status in 309 ICU pts with AKI

Nutritional status by SGA (Subjective Global Assessment of nutritional status, Baker JP et al., NEJM 1982; 306:969-72)

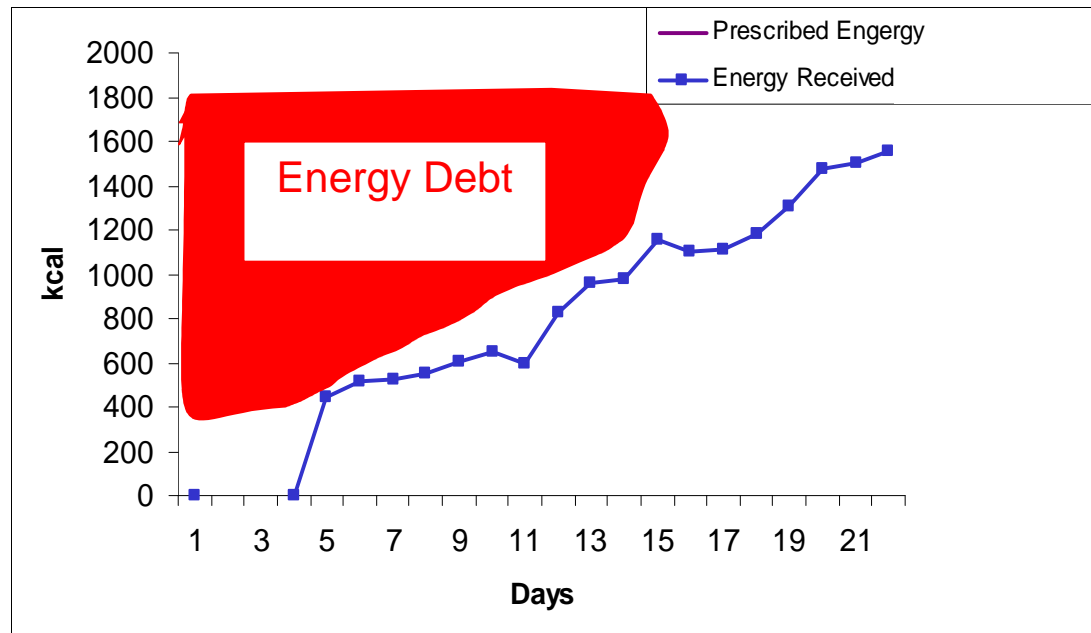
Figure 2. In-hospital mortality according to nutritional status. □, normal nutritional status; ▨, moderate malnutrition or risk of malnutrition; ■, severe malnutrition. χ^2 for trend ($P < 0.001$). * $P < 0.001$



Mechanisms of underfeeding in AKI



The concept of protein/energy debt in the ICU and its negative impact on outcome



■ Energy (and protein) debt is associated with:

- ↑ ICU LOS
- ↑ Days on MV
- ↑ Complications
- ↑ Mortality

Rubinson L et al., CCM 2004; 32:350-357

Villet S et al., Clin Nutr 2005; 24:502-509

Dvir D et al., Clin Nutr 2006; 25:37-44

Petros S et al., Clin Nutr 2006; 25:51-59



Nutrition Support among Critically Ill Children with AKI

Ursula G. Kyle, Ayse Akcan-Arikan, Renán A. Orellana, and Jorge A. Coss-Bu

- In patients with AKI the overall protein provision (19% [0%–60%]) was lower than energy provision (55% [22%–113%]) compared with estimated needs (P,0.001)
- Patients with AKI were more likely to be fasted versus receiving enteral/parenteral nutrition, and to receive less than 90% of BMR than no AKI patients

Clin J Am Soc Nephrol 8: 568–574, 2013.



Protein/Energy Debt in Critically Ill Children in the Pediatric Intensive Care Unit: Acute Kidney Injury As a Major Risk Factor

✉ Alice Sabatino, RD, Giuseppe Regolisti, MD, Umberto Maggioni, MD, PhD, and Enrico Fiaccadori, MD, PhD

Criteria for Selecting Patients That Would Benefit the Most From Indirect Calorimetry in PICU

- Underweight and overweight patients
 - Weight gain >10% during PICU stay
 - Failure to meet prescribed caloric goals (>90%)
 - Failure to wean or increased dependency of mechanical ventilation
 - Require the use of muscle relaxant for >7 d
 - Neurologic trauma with evidence of dysautonomia
 - Oncologic diagnoses
 - Mechanical ventilation for >7 d
 - Suspicion of severe hypermetabolism or hypometabolism
 - PICU length of stay for >4 wk
-



Conclusion

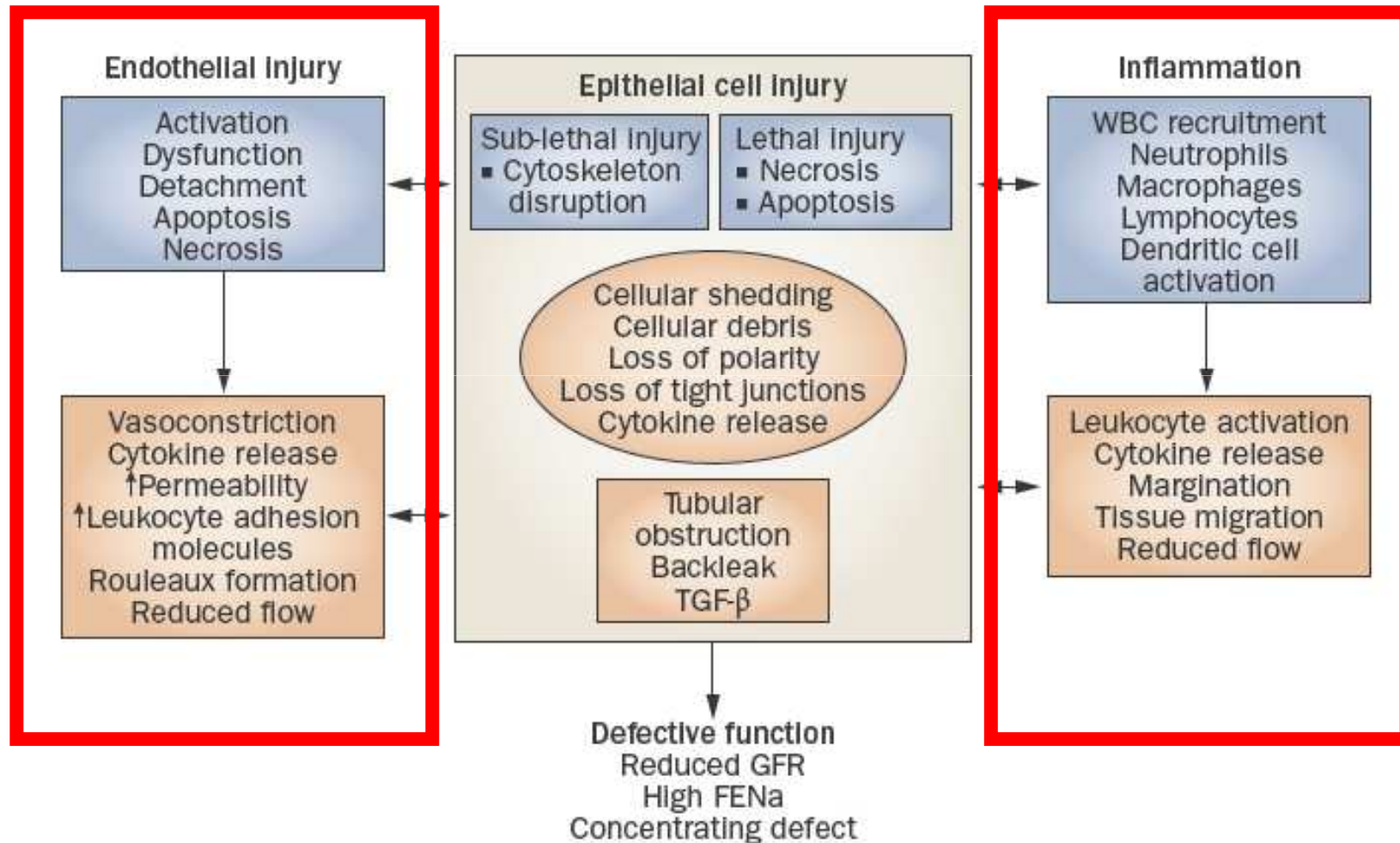
- AKI in pediatric patients at risk is common, and is associated with increased morbidity and mortality
- AKI is now viewed as an inflammatory process activated by ischemia-reperfusion injury
- AKI is associated with an increased risk for progression to CKD
- An integrated therapeutic approach based on supportive therapy, adequate nutrition and RRT is needed

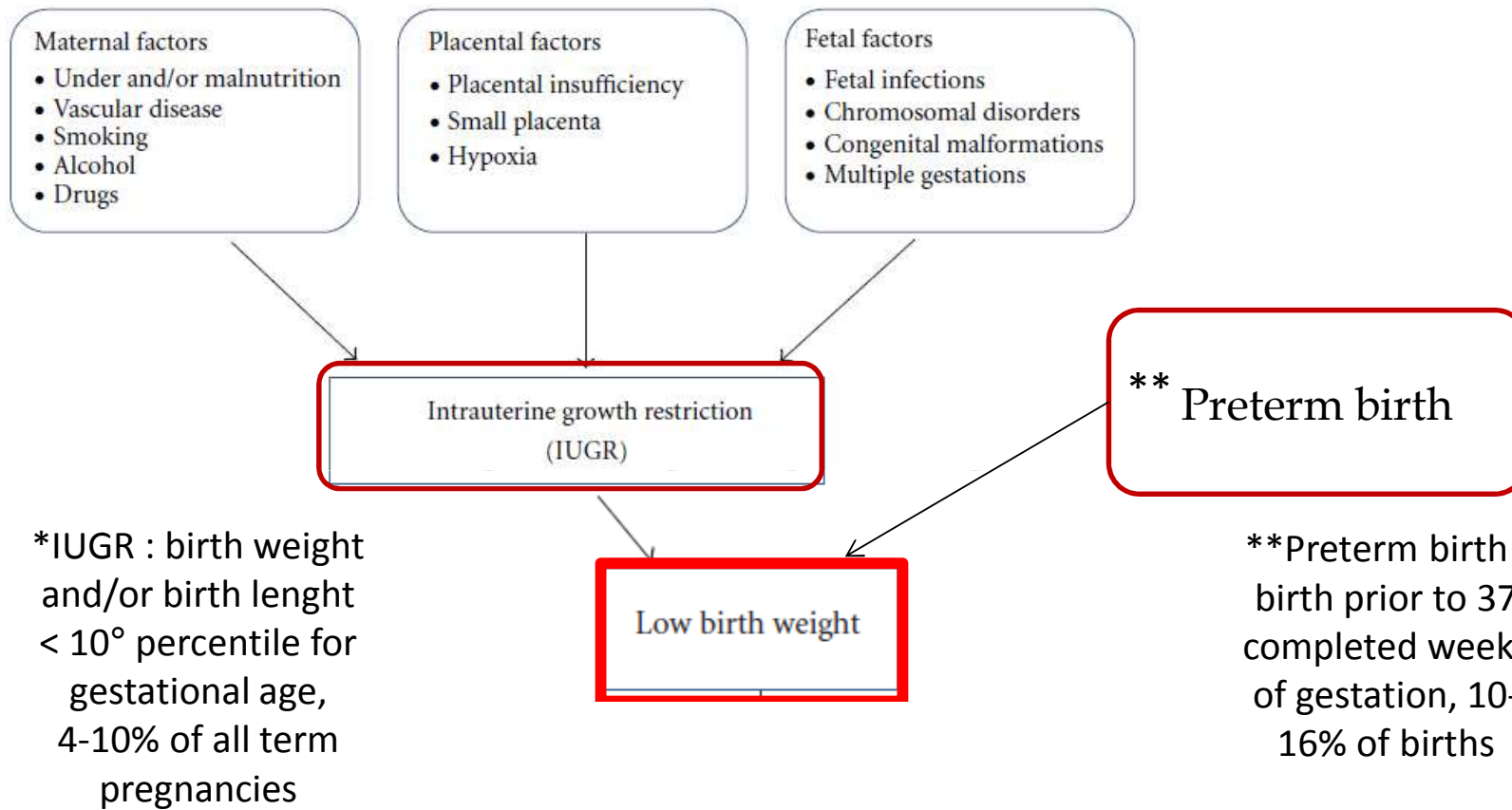
Table 1. Schwartz estimated creatinine clearance equation

Age	<i>K</i>
≤1 year	
low birth weight	0.33
full term	0.45
2 to 12 years	0.55
13 to 21 years	
female patients	0.55
male patients	0.7

$e\text{CCl} (\text{ml}/\text{min per } 1.73 \text{ m}^2) = K \times \text{length (cm)}/\text{serum creatinine (mg/dl)}$. *K*, age-specific proportionality constant.

The complex interactions between different renal cells in the pathogenesis of ischemic AKI





Risk factors for AKI in neonates

- VLBW (500-1500 gr)
- Congenital heart disease
- ECMO
- Perinatal depression

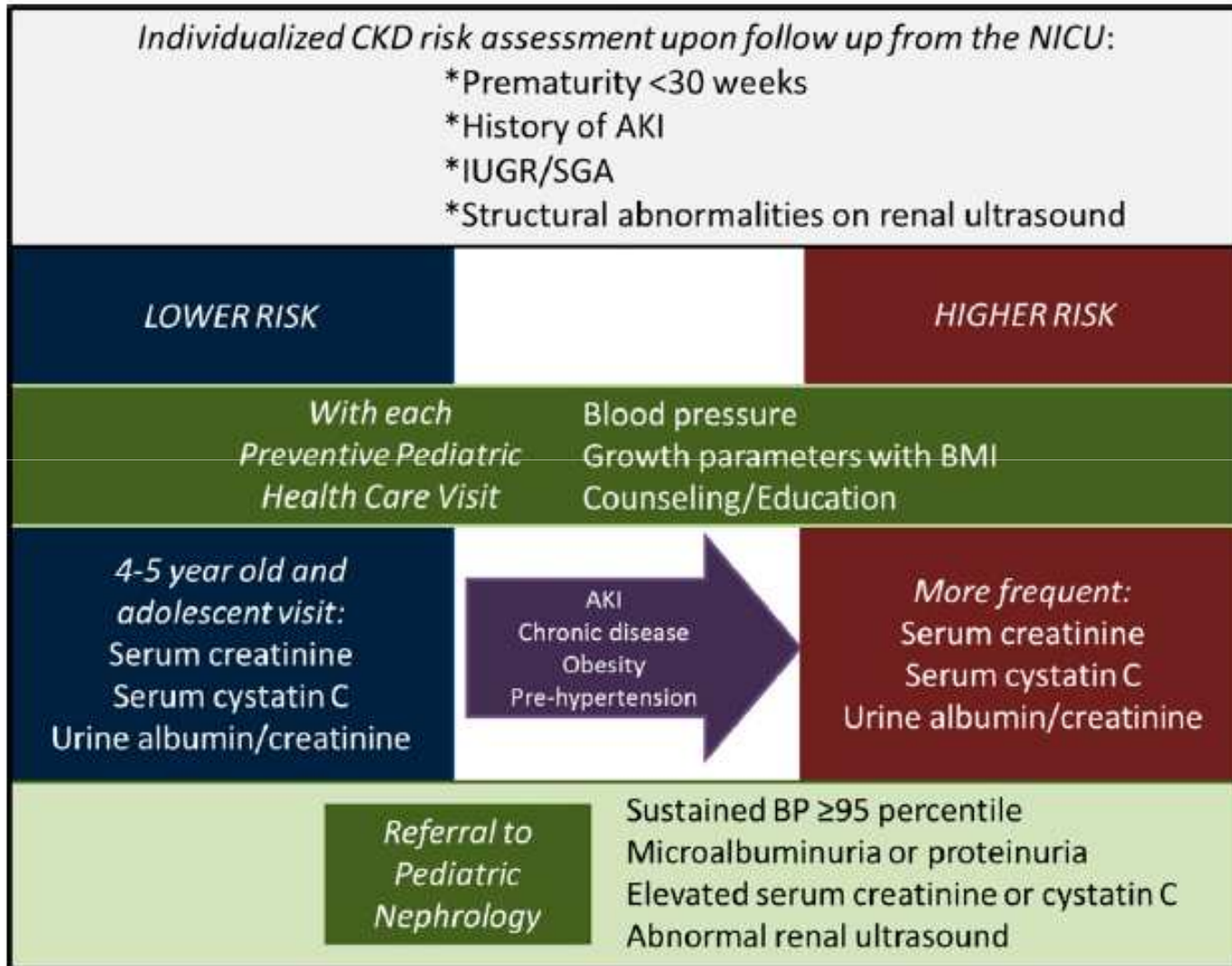
Prematurity

- Worldwide almost 13 millions infants are born prematurely each year
- About 80-90% of infants born 501 to 1500 g survive to NICU discharge
- 60% of survivors leave the NICU without any major neonatal morbidity

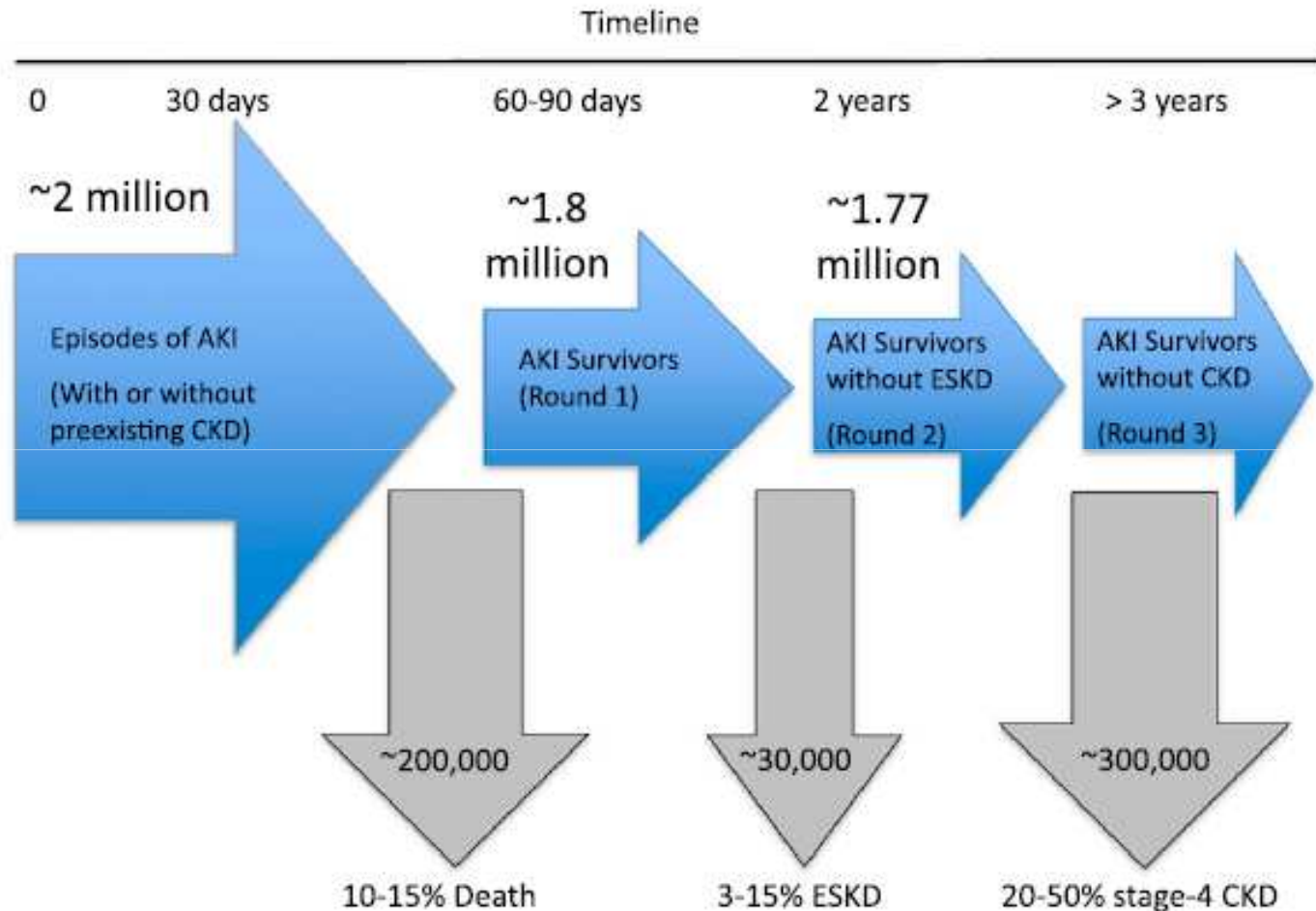
Beck S et al., Bull World Health Organ 2010; 88:31-38
Horbar JD et al., Pediatrics 2012; 129:1019-26



Follow up strategies for NICU survivors



Estimates of AKI burden in developed countries and outcomes of survivors.



Renal Glomeruli and Tubular Injury Following Indomethacin, Ibuprofen, and Gentamicin Exposure in a Neonatal Rat Model

ALISON L. KENT, LESLEY E. MAXWELL, MARK E. KOINA, MICHAEL C. FALK, DAVID WILLENBORG,
AND JANE E. DAHLSTROM

Pediatr Res 2007; 62: 307–312

Acute kidney injury in non-critically ill children treated with aminoglycoside antibiotics in a tertiary healthcare centre: a retrospective cohort study

Michael Zappitelli¹, Brady S. Moffett², Ayaz Hyder³ and Stuart L. Goldstein⁴

Nephrol Dial Transplant (2011) 26: 144–150



Prematurity and the kidney

The entity of preterm birth itself may result in morphological and functional alterations associated with negative long term renal outcomes:

- Reduced nephron number
- Reduced renal volume
- Hypertension
- Proteinuria

Shalloh C et al., *Transl Res* 2012; 159:80

Duncan AF et al., *Ped Nephrol* 2011; 26:1115

Kejzer-Veen MG et al., *Ped Nephrol* 2010; 25:499



3–5 year longitudinal follow-up of pediatric patients after acute renal failure

DJ Askenazi¹, DI Feig^{1,2}, NM Graham³, S Hui-Stickle¹, SL Goldstein^{1,4}

Among the 29 patients assessed for long-term sequelae at 3–5 years, 17/29 (59%) subjects had at least one sign of renal injury (microalbuminuria, hyperfiltration, hypertension, decreased GFR)

A pediatric nephrologist was involved in care of only 6/17 (35%) with chronic renal injury

Kidney International (2006) **69**, 184–189.



The majority of pediatric patients with AKI are discharged from the hospital with «normal» serum creatinine levels

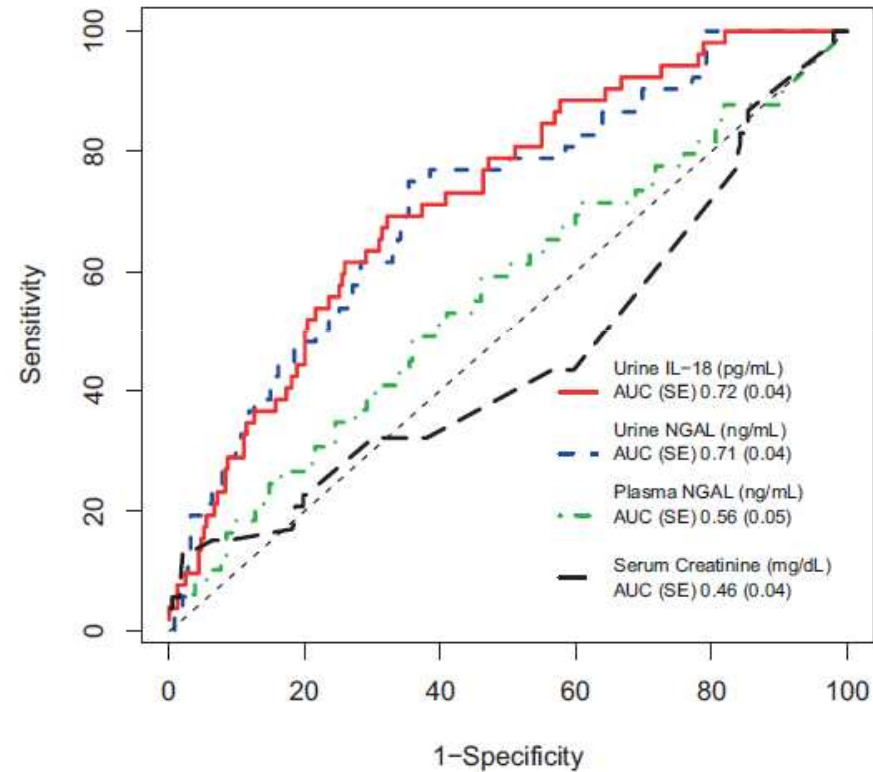
TABLE 2 Estimates of GFR With “Normal” Creatinine Values for a Hypothetical 2-Year-Old Child With Height 86.4 cm Using the Revised Schwartz Equation^a

Serum Creatinine (mg/dL)	Estimated GFR (mL/min/1.73 m ²)	Interpretation ^{148,150}
0.3	119	Normal
0.4	89	Normal
0.5	71	Stage 2 CKD
0.6	59	Stage 3 CKD

^a GFR = 0.413 × height(cm) / creatinine(mg/dL).¹⁴⁸



Postoperative Biomarkers Predict Acute Kidney Injury and Poor Outcomes after Pediatric Cardiac Surgery



J Am Soc Nephrol 22: 1737–1747, 2011.

Developing nephrons are particularly vulnerable to maldevelopment and dysfunction in an ex-utero environment

- **Low birth weight**
- **AKI in neonates**



Epidemiology of neonatal AKI

Recent Estimates of AKI Incidence in Various Neonatal Populations

Study	Study Population	AKI Definition	Number of Infants	AKI Incidence
Viswanathan et al ¹⁴¹	Extremely LBW (<1000 g)	Serum creatinine \geq 1.5 mg/dL or urine output <1 mL/kg/h	472	12.5%
Koralkar et al ¹⁴²	Very LBW (<1500 g)	AKIN ⁶⁶	229	18%
Selewski et al ¹⁴⁵	Asphyxiated newborns undergoing therapeutic hypothermia	AKIN	96	38%
Kaur et al ¹⁴⁴	Infants \geq 34 wk gestation with asphyxia (Apgar <7 at 1 min after birth)	AKIN	36	41.7%
Blinder et al ¹⁴⁵	Infants <90 d old with congenital heart disease undergoing surgery	AKIN	430	52%
Gadepalli et al ¹⁴⁶	Infants with congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation	RIFLE ¹⁴⁷	68	71%

AKIN, Acute Kidney Injury Network; RIFLE, risk, injury, failure, loss, end-stage renal disease.

PEDIATRICS Volume 131, Number 6, June 2013



Mandatory fluid intake in the ICU

- Resuscitation fluids
- Blood products
- Drug vehicles
- Enteral nutrition
- Parenteral nutrition



FO negatively affects GFR and increase the risk of AKI

Venous congestion reduces the glomerular net filtration pressure
pressure → glomerular filtration rate is reduced

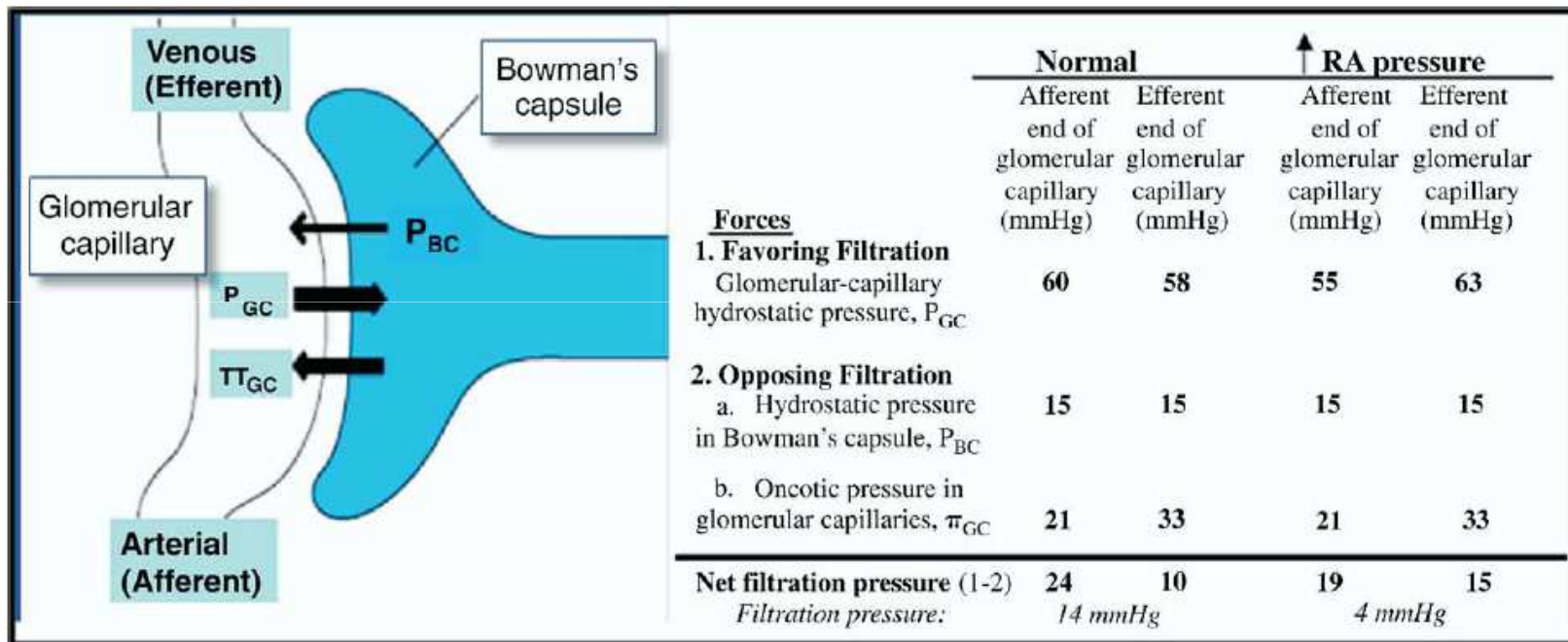


Figure 1 Impact of Venous Congestion on Glomerular Net Filtration Pressure

An illustration of the afferent and efferent pressures at a glomerular capillary in a patient with normal hemodynamics and a patient with increased right atrial (RA) pressure and venous congestion. P_{BC} = hydrostatic pressure in Bowman's capsule; P_{GC} = glomerular capillary hydrostatic pressure; π_{GC} = oncotic pressure in glomerular capillaries.



Defining reduced urine output in neonatal ICU: importance for mortality and acute kidney injury classification

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Lara Cavalcante Vaz Cunha²
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UNIFOR, Fortaleza, Ceará, Brazil and

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Universidade Federal do Ceará, Fortaleza, Ceará, Brazil

Conclusions. UO is a predictor of mortality in NICU. An association between a UO threshold < 1.5 mL/kg/h and mortality was observed, which is higher than the previously published pRIFLE thresholds. Adopting higher values of UO in pRIFLE criteria can improve its capacity to detect AKI severity in neonates.



A systematic review of RIFLE criteria in children, and its application and association with measures of mortality and morbidity

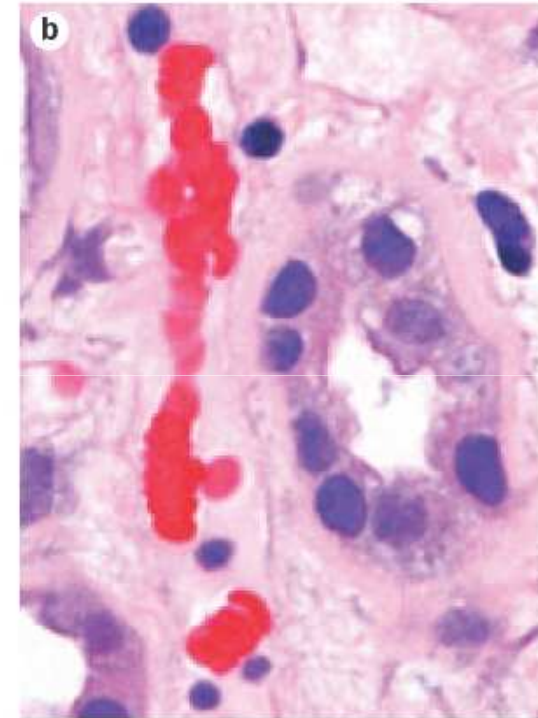
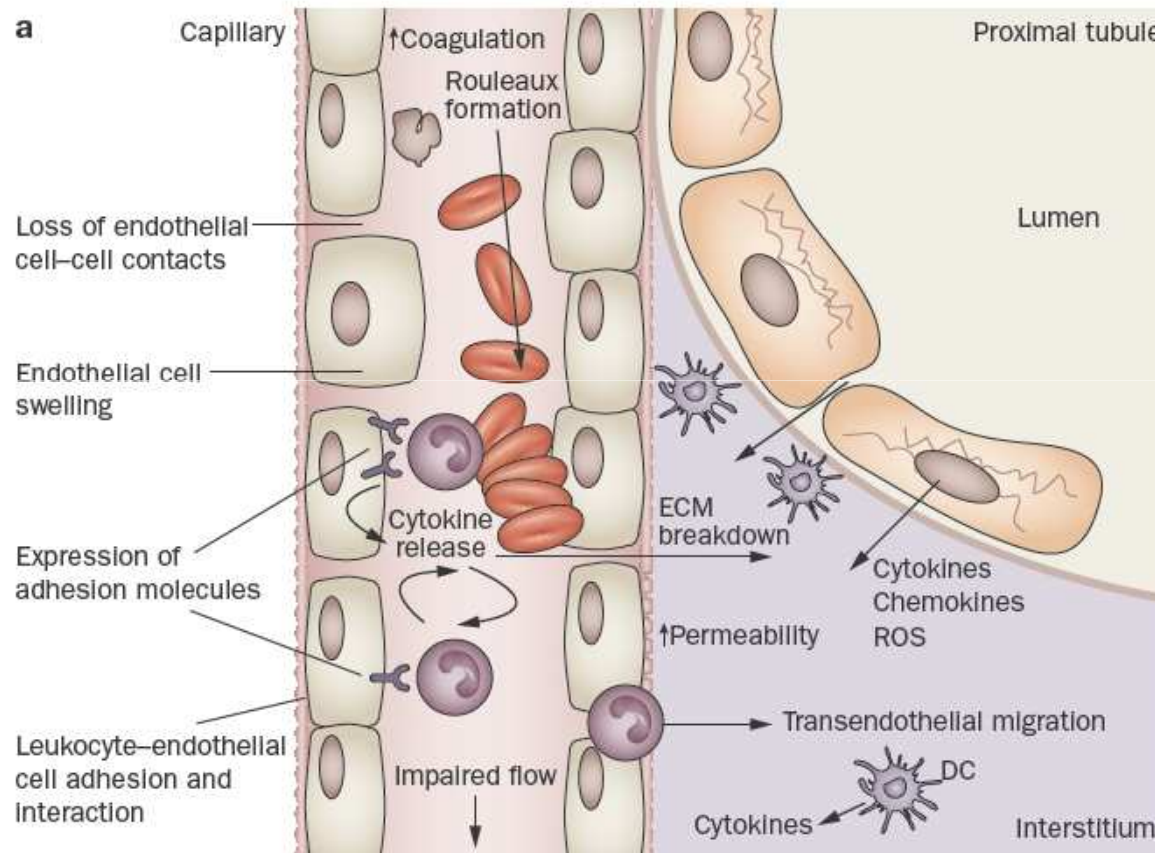
Morgan B. Slater^{1,2,3}, Vijay Anand¹, Elizabeth M. Uleryk⁴ and Christopher S. Parshuram^{1,2,3,5,6,7}

Thus, although the RIFLE was developed to improve the consistency of defining acute kidney injury, there are still major discrepancies in its use in pediatric patients that may undermine its potential utility as a standardized measure of acute kidney injury in children.

Kidney International (2012) **81**, 791–798;

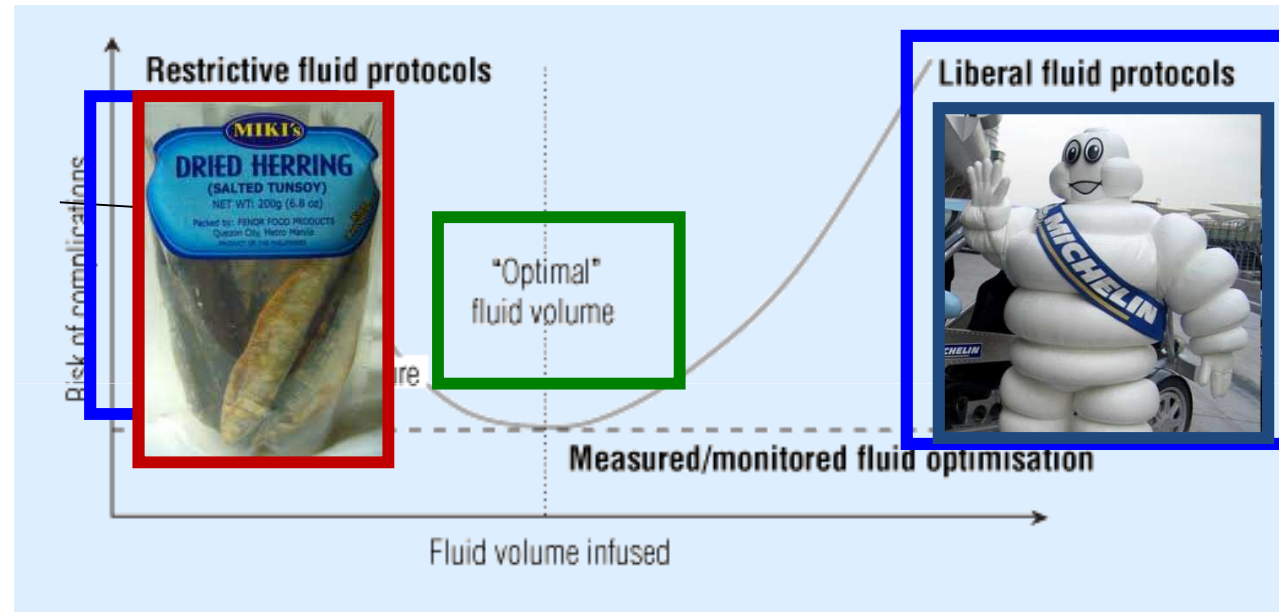


Endothelial activation, injury and reduced microvascular flow in AKI



The dose-response curve of fluids vs complications: two deadly extremes of the same problem

Hypothetical curve of the risk of fluid therapy-related complications versus volume of fluid infused



Risk is associated with both persistent hypovolaemia and iatrogenic fluid overload, although the actual and relative risks of these two extremes may be difficult to quantify in individual patients. Restrictive and liberal fluid protocols aim to minimise the risks of fluid overload and hypovolaemia, respectively. However, by failing to take into account individual patient differences, these protocols may produce their own complications. Monitored fluid administration individualises fluid requirements but, given the lack of an ideal monitor for volume replacement, does not necessarily determine the optimal fluid volume to minimise risk. (Figure adapted from Ayus and Arieff.¹⁹)

