Differential Diagnosis of AKI: Can Biomarkers Help?

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Group 2

Use of biomarkers for differential diagnosis of AKI in clinical practice

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AKI Biomarkers in Differential Diagnosis

:

Questions	**AKI Biomarkers Useful?**
• Is it AKI?	□□□□
• Cause?	□□ + Contextual BMs
• Stage of AKI?	□□
• Phase of AKI?	□□ Potential
• Treatment?	□□ Selection, Monitor

Biomarkers question our understanding of renal pathophysiology and require us to reclassify AKI now and in the future

Statement 3-Goldstein

- Etiology of AKI should be determined as soon as the diagnosis is made. Functional and damage biomarkers should be used to help differentiate AKI of uncertain etiology.

ADQI: Biomarker Classification of AKI

Function

= "No-AKI"

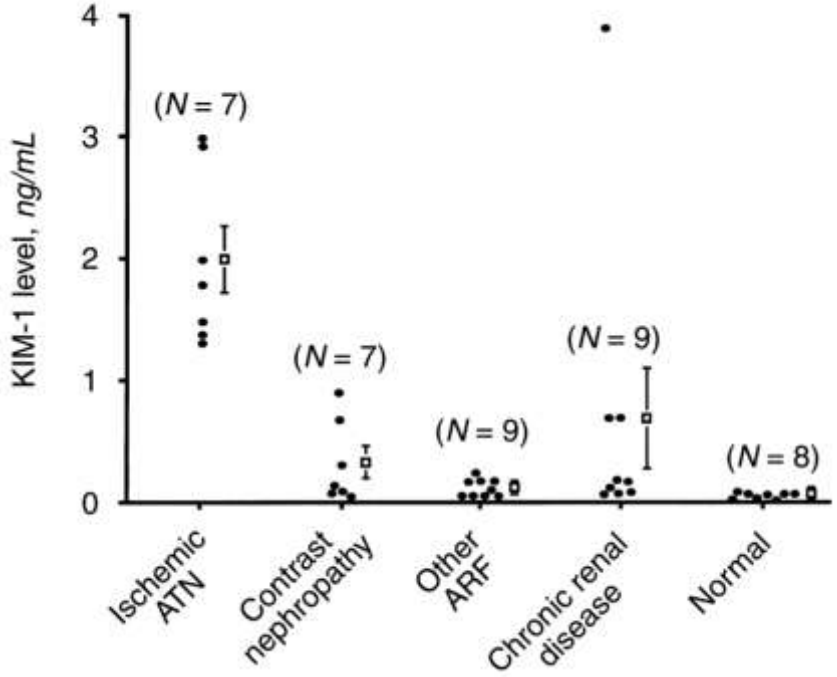
Structure	**NO CHANGE**	**+ CHANGE**
NO DAMAGE	- -	+ -
+ DAMAGE	- +	+ +

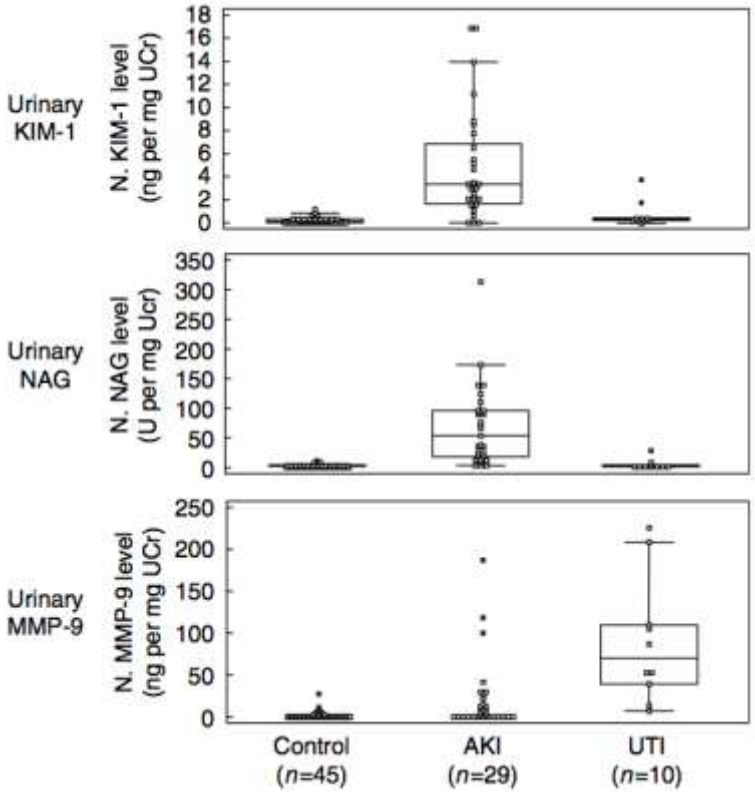
= "Functional AKI"

BM+ Cr- = "Renal Injury "

Structural and Functional Injury

In established AKI, injury biomarkers distinguish Ischemic Injury





Han, *Kidney Int* 2001; 62: 237

Han, *Kidney Int* 2008; 73: 863

Statement 2-ADQI-Group 2

- The terms functional change and kidney damage should be used in preference to the terms pre-, intra- and post-renal in order to narrow the differential diagnosis of AKI.

DD of Pre-renal and intrinsic AKI suggests reduced severity of structural injury associated with earlier recovery

Patients were classified as ‘prerenal’ when:

- caused by factors that compromise renal perfusion, and
- Cr returned to baseline with volume repletion or improvement in cardiac output **within 3 days of directed therapy**.
- Even after careful post-hoc adjudication **26%** unclassifiable!

Singer Kidney Int 2011: 80: 405

Pre-Renal AKI

- Definition is problematic
- Reversible, Volume sensitive…

Transient AKI

- common in hospital patients,
- Austin Hospital: 2000 – 2002 ; n =20,126
- 3641 AKI:
  - 1600 recovered prior to discharge = T-AKI (= one third of all cases):
    - 40% within 24hr,
    - 73% within 72hr
- T-AKI independently associated with mortality

Uchino et al NDT 2010; 25:1833

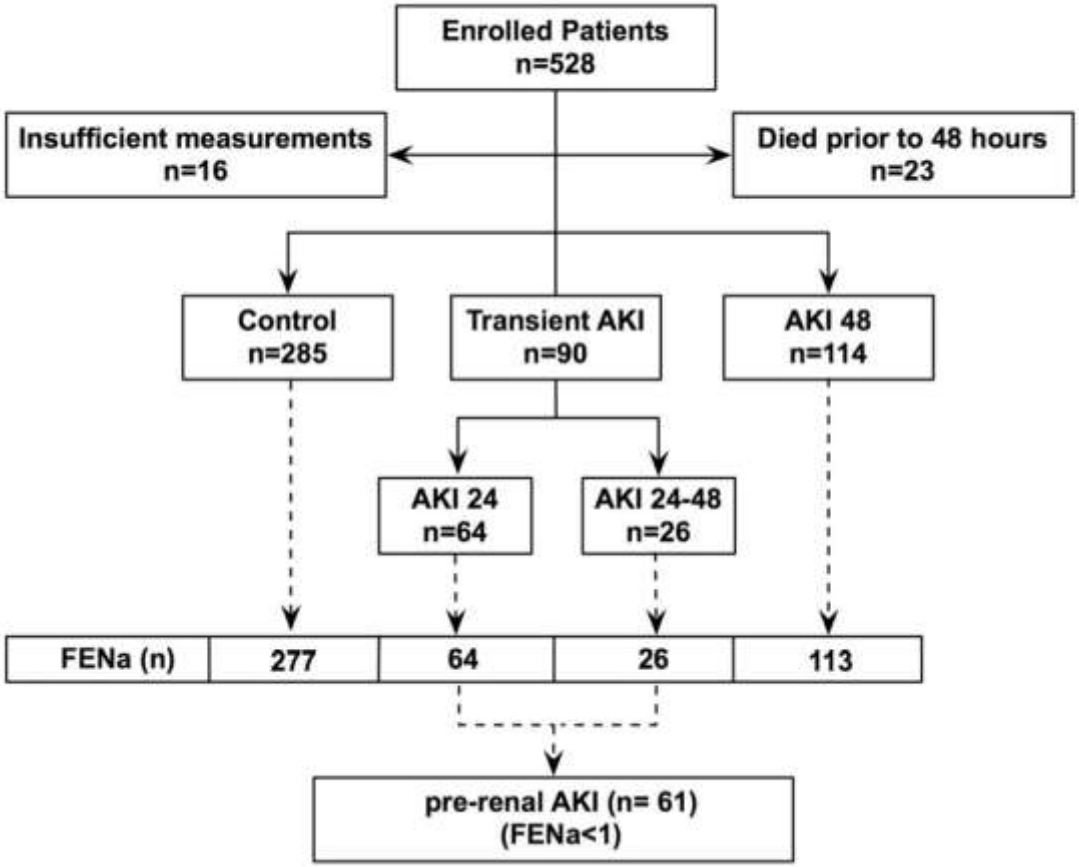
Pre-Renal AKI vs TAKI

- AKI (AKIN): Cr 0.3mg/dl increase <48 hrs
- *Transient* AKI(TAKI): <24, 24-48hrs
- Established AKI: >48hrs
- Pre-renal AKI:
  TAKI + preservation of tubular function

  Preserved tubular function: FENa<1.0

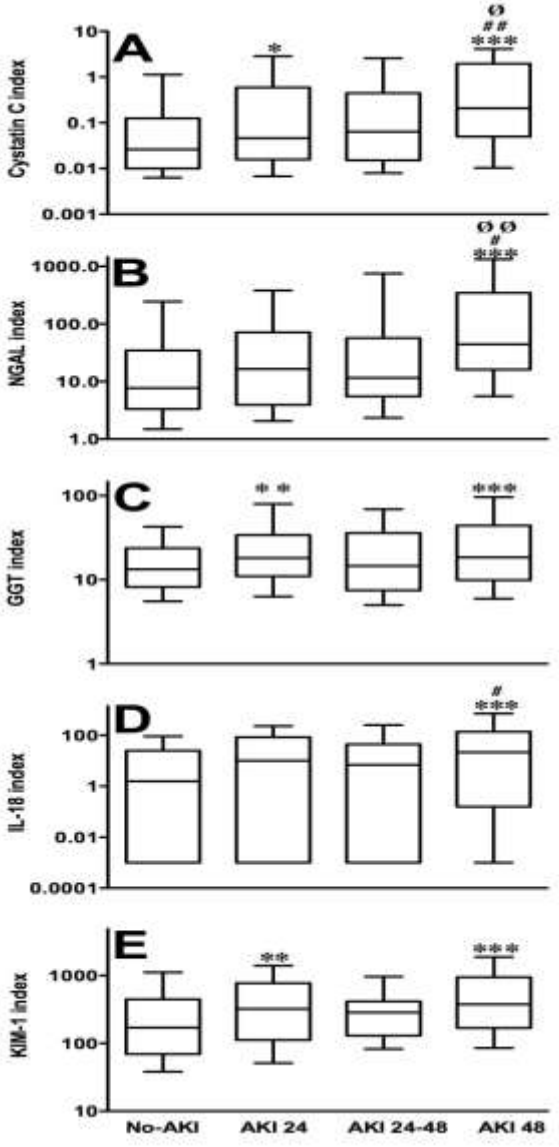
Nejat, Pickering, Devarajan,Bonventre, Edelstein, Walker, Endre. Kidney Int 2012 in pr

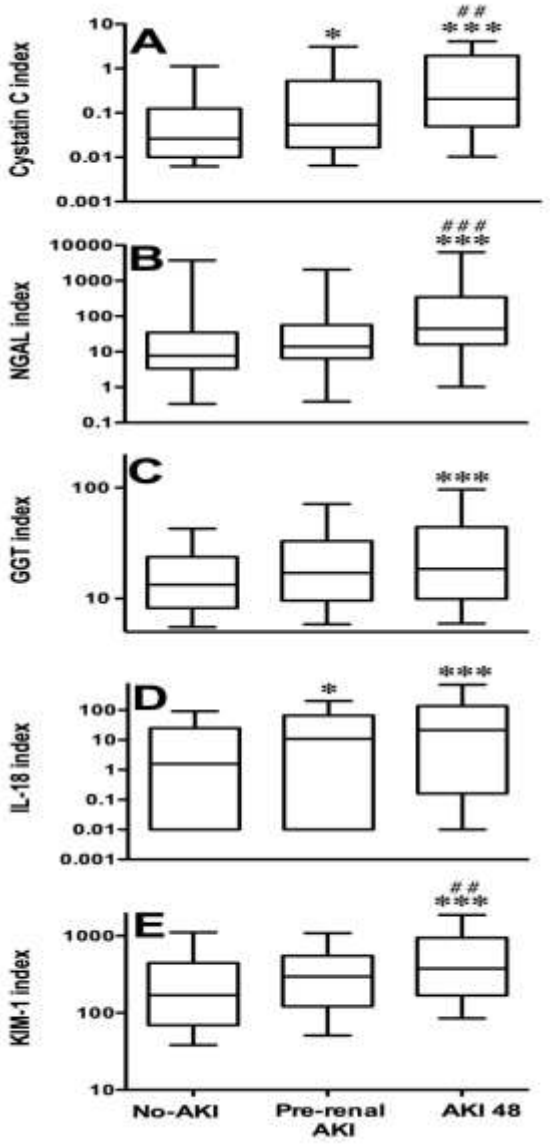
Are Biomarkers increased in Pre-renal AKI?



Nejat, Pickering, Devarajan,Bonventre, Edelstein, Walker, Endre. Kidney Int 2012 in pr

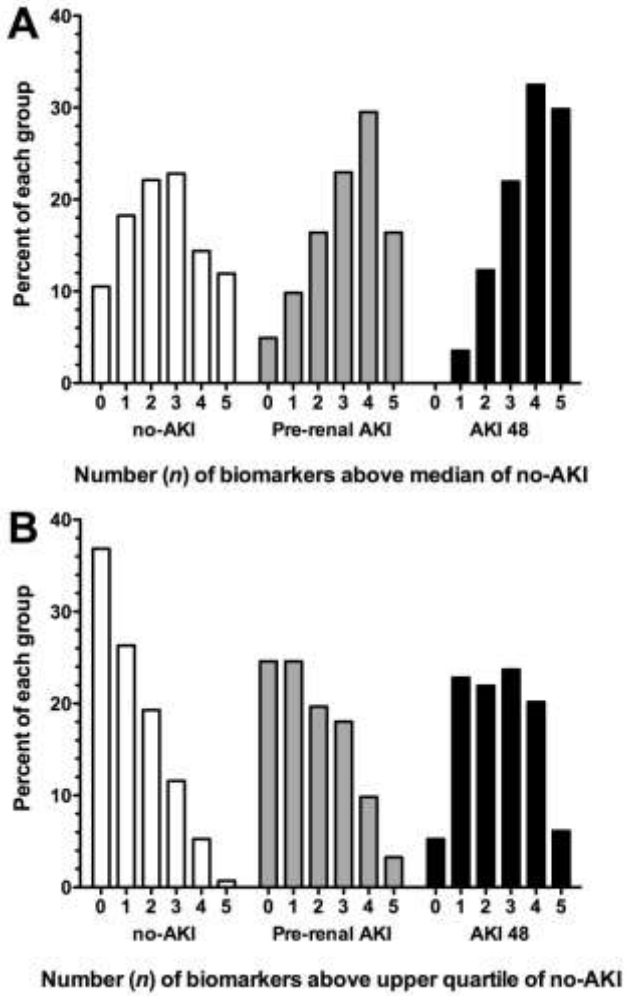
BM increase with duration and severity





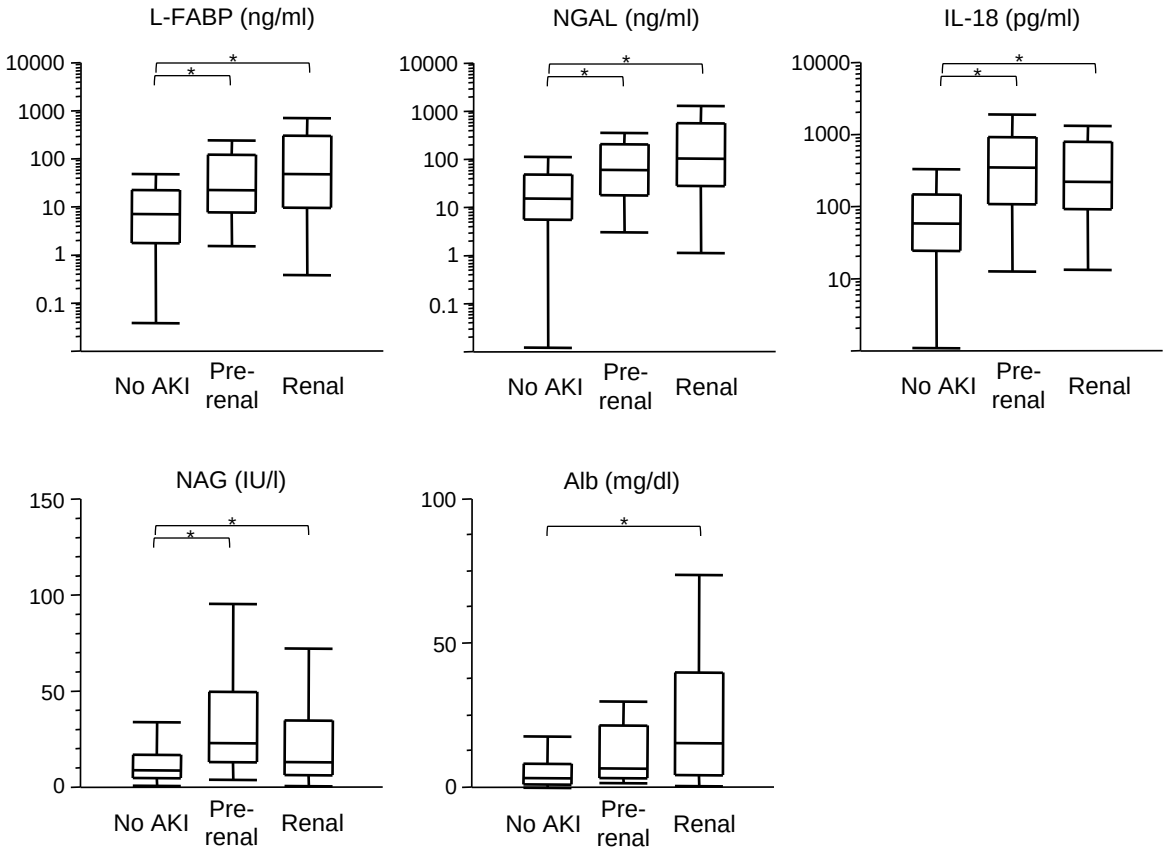
Nejat, Pickering, Devarajan,Bonventre, Edelstein, Walker, Endre. *Kidney Int* 2012 in press

Biomarker Distribution in Pre-renal AKI = established AKI



Nejat, Pickering, Devarajan,Bonventre, Edelstein, Walker, Endre. *Kidney Int* 2012 in pr

Biomarkers of AKI in “pre-renal AKI” in a mixed ICU



Doi K and Noiri E, Univ of Tokyo

Table III

The effect of dehydration on the kidney function of subject J.N.

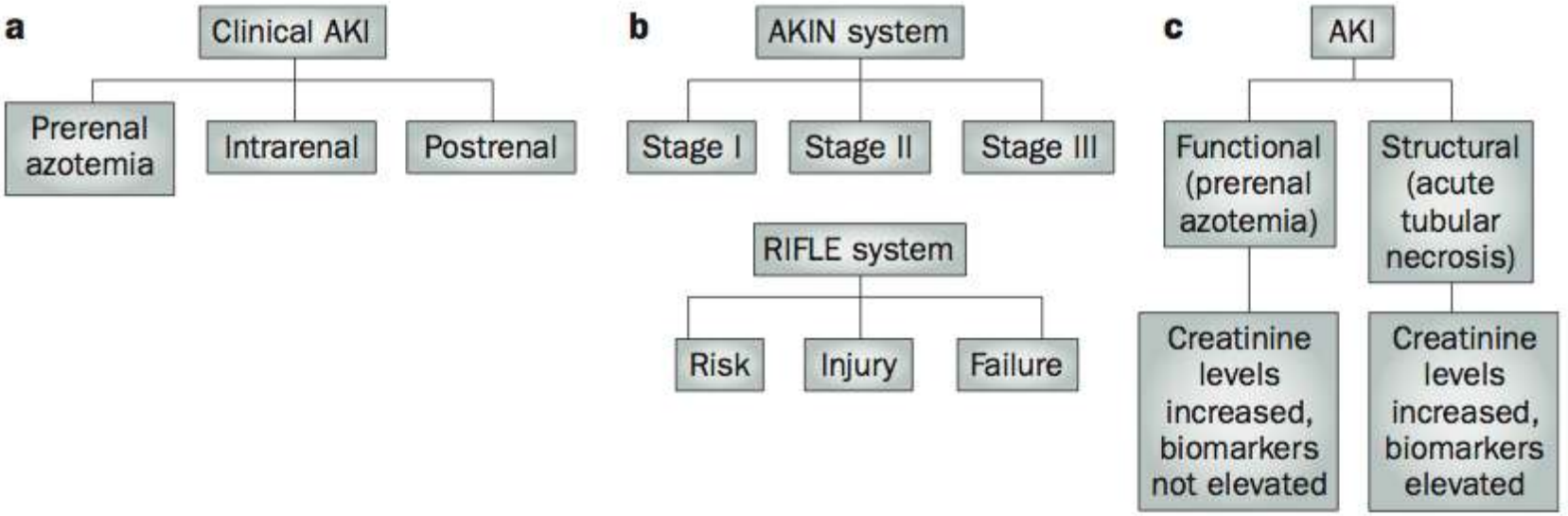
DATE. 1935		WATER OF URINE GM.	SP.GR. OF URINE	TOTAL SOLIDS OF URINE GM.		NITROGEN OF URINE GM.		PRESENCE IN URINE OF PROTEIN	CASTS	RBC.
PRELIMINARY PERIOD.										
FEB.	18	1274	1.015	40.8				0	0	0
	19	1431	1.012	41.2	AV.40.1					
	20	1151	1.019	39.2						
	21	1433	1.015							
	22	1448	1.013			10.30				
	23	1012	1.016			8.70	AV.9.31			
	24	1031	1.016	39.1		9.46		0	0	0
	25	1102	1.016			8.80		0	0	0
DEHYDRATION PERIOD										
FEB.	26	472	1.031	31.8		6.32		0	0	0
	27	481	1.032	36.6	RETENTION	7.00	RETENTION	0	0	0
	28	442	1.037	38.0	9.9	8.08	5.20	SL.TR.	+	0
MAR.	1	446	1.038	44.1		10.64		TRACE	+	+
			1.041							
RECOVERY PERIOD.										
MAR.	2	742	1.024	48.1	- EXCESS 8.0	14.48	- EXCESS 5.17	SL.TR.		
	3	1586	1.016	40.8		10.32		SL.TR.		
	4							SL.TR.		
	5							0	0	0

Coller & Maddock Annals Surg 1935;102:94

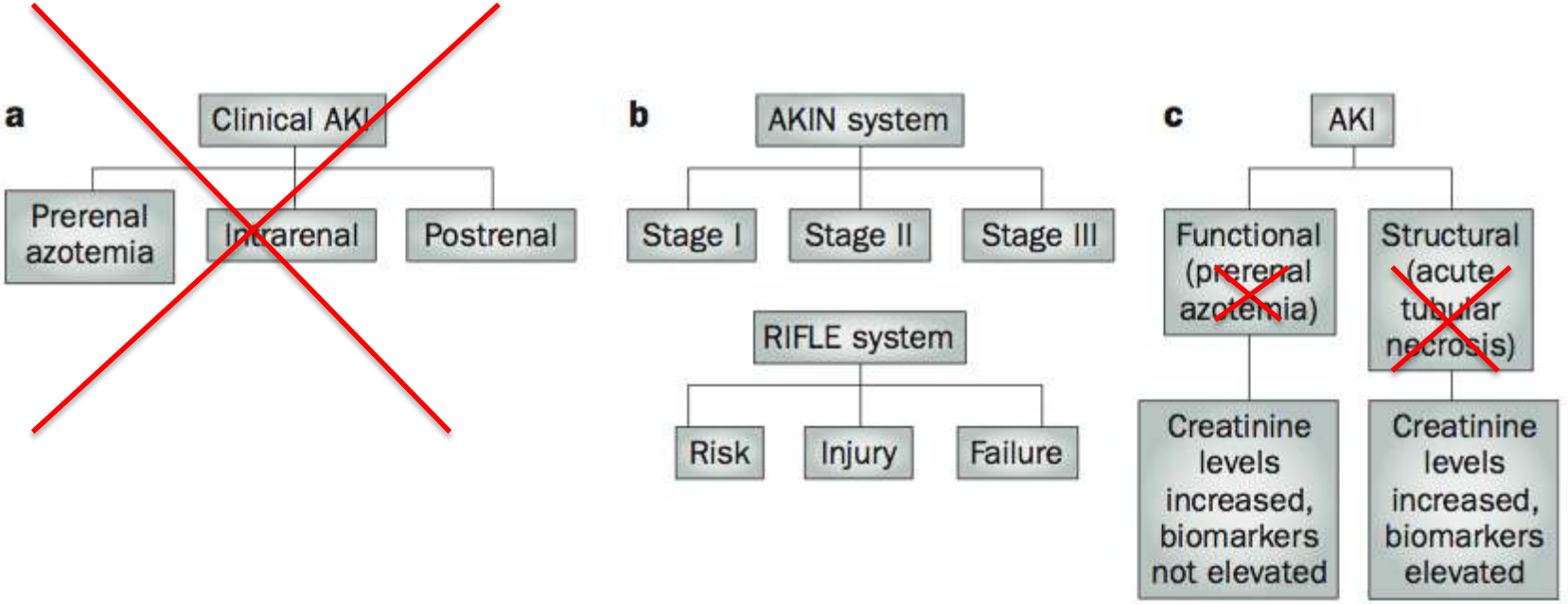
Pre-renal AKI

- Biomarkers of Injury are increased
- adverse outcomes occur and relate to duration and severity
- the milder end of a continuum of injury
- separation not clinically useful, may delay investigation or treatment
- Just a cause, not a type of AKI

DD or Classification?



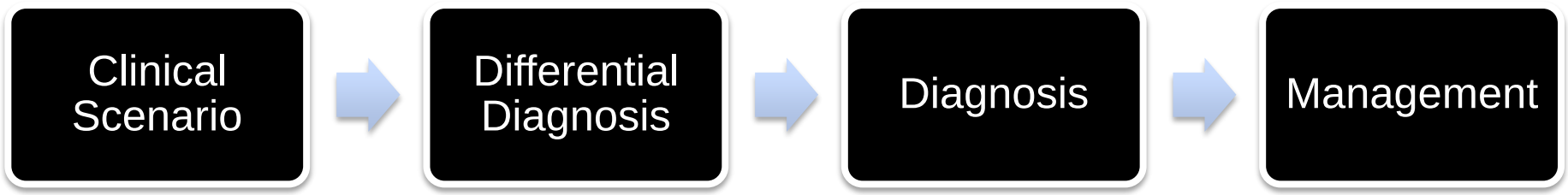
Parikh & Coca *Nature Reviews Nephrology*, 2010; 6: 64



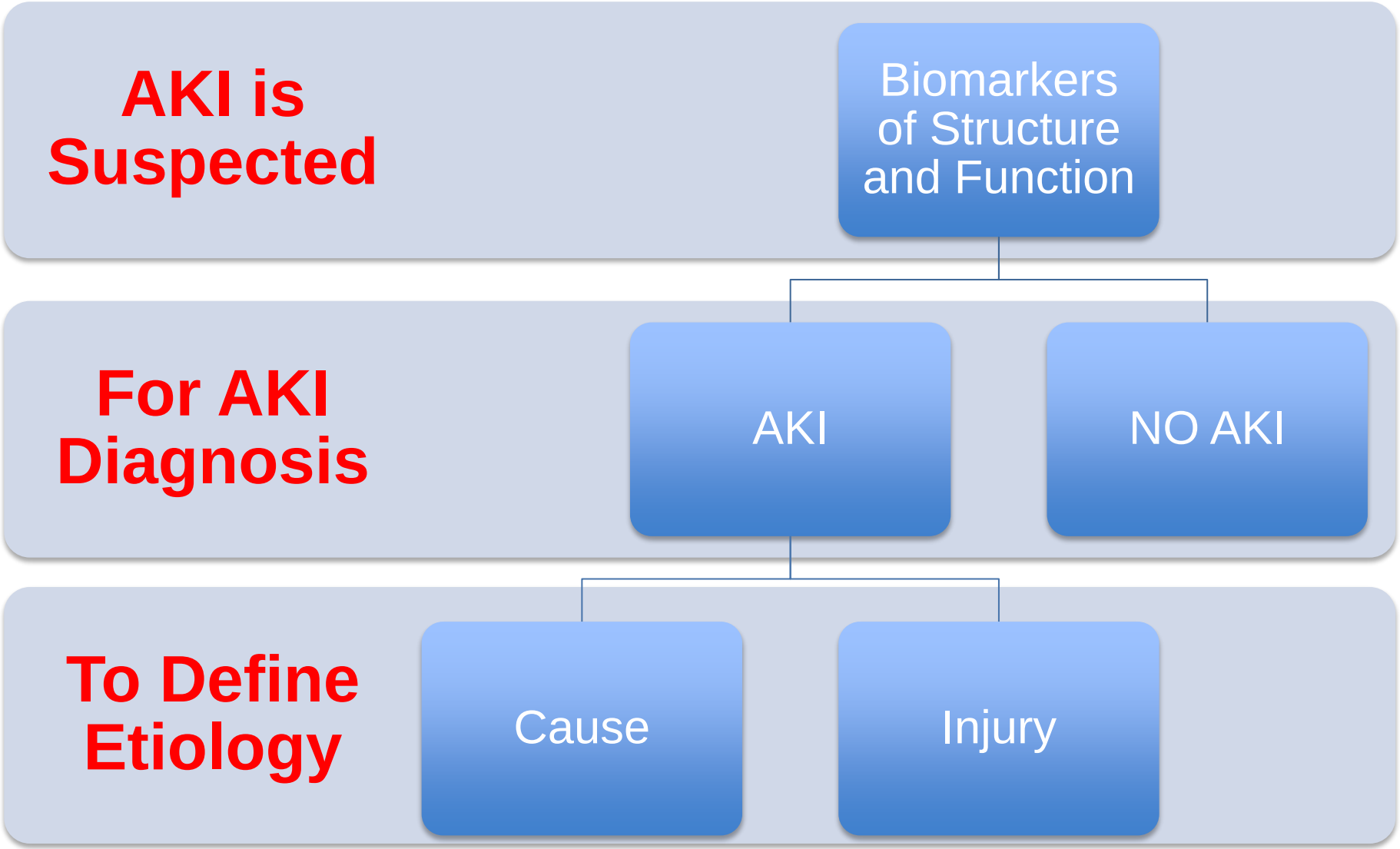
Maps to Severity (Misses Duration)

Maps Actual Events (Misses Duration)

Parikh & Coca *Nature Reviews Nephrology*, 2010; 6: 64


Clinical Scenario
Differential Diagnosis
Diagnosis
Management

At Risk Patient - Use Biomarkers When:



AKI Causes- KDIGO 2011

Selected Causes Requiring Immediate Diagnosis and Specific Therapy	Recommended Diagnostic Tests
Decreased Kidney Perfusion	Volume Status and urinary diagnostic indices
Acute glomerulonephritis, vasculitis, interstitial nephritis, thrombotic microangiopathy	Urinary sediment examination, serologic and hematologic testing
Urinary tract obstruction	Kidney ultrasound

“it is axiomatic that patients always be managed according to the cause of their disea
and thus it is important to determine the cause of AKI whenever possible.”

Decreased Kidney Perfusion

- Volume status *may be* unhelpful
- Urinary indices *are* unhelpful
- Renal perfusion is almost never measured
- Cardiac output, and renal venous pressure are usually ignored
- Assumption that “pre-renal AKI is a unique functional state that recovers without sequelae” *is false*

Statement 7-ADQI- Group 2

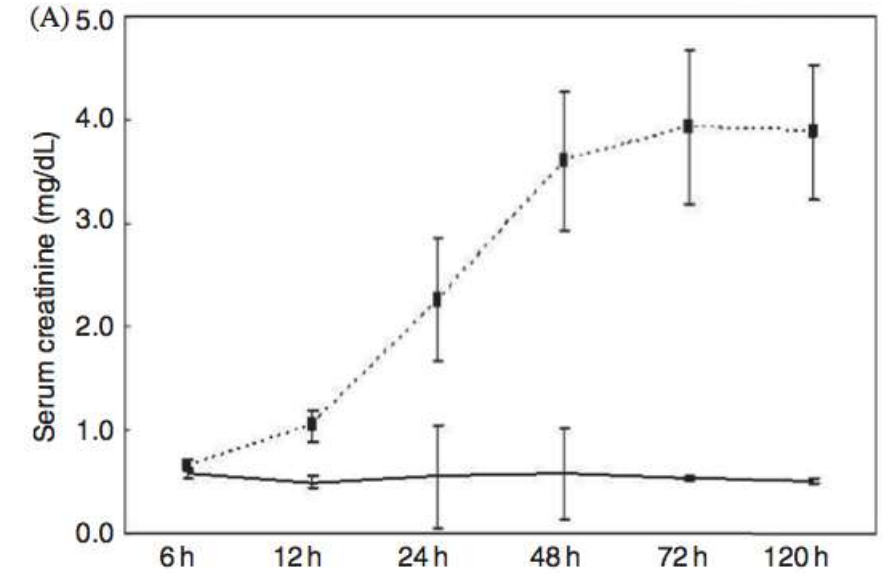
- Consider biomarkers from other organs in the context of determining the etiology

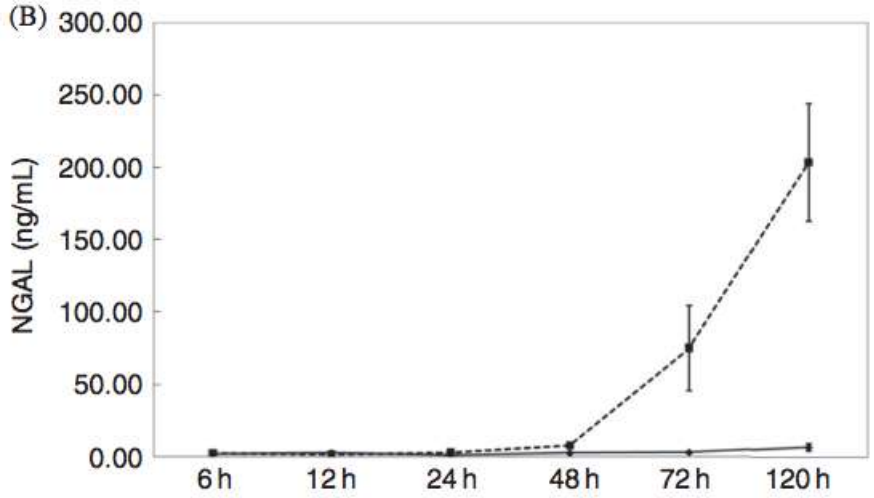
- Research Recommendation: Studies of biomarkers from other organs are recommended in conditions where AKI is clearly secondary, e.g. cardio-renal syndrome

Context of Risk is Important

Clinical Presentation	Cardiac Failure	Hepatic Failure	Sepsis
Context Specific Biomarkers	BNP, Pro-BNP	Bilirubin, Hepatic Enzymes	PCT, Culture
Primary Diagnosis	✔	✔	✔
Renal Structure and Function Biomarkers	✚	✚	✚
		AKI Complicating Primary Diagnosis	

BMs performance is modulated by Cause:

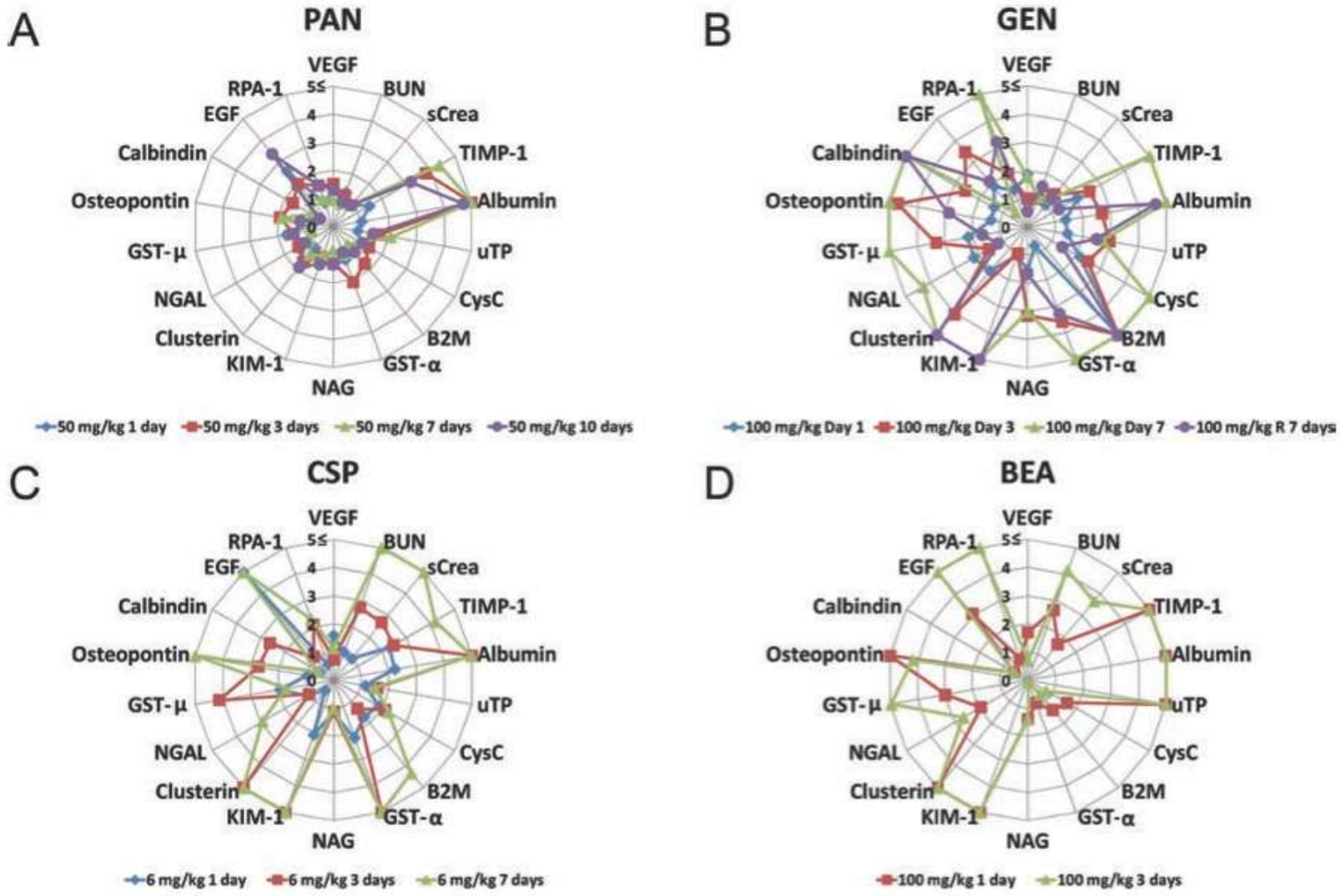




Paraquat
Gil, et al (2009).
Clinical Toxicology, *47*: 870)

BMs distinguish Nephrotoxins

BM profiles vary with site and cause of injury

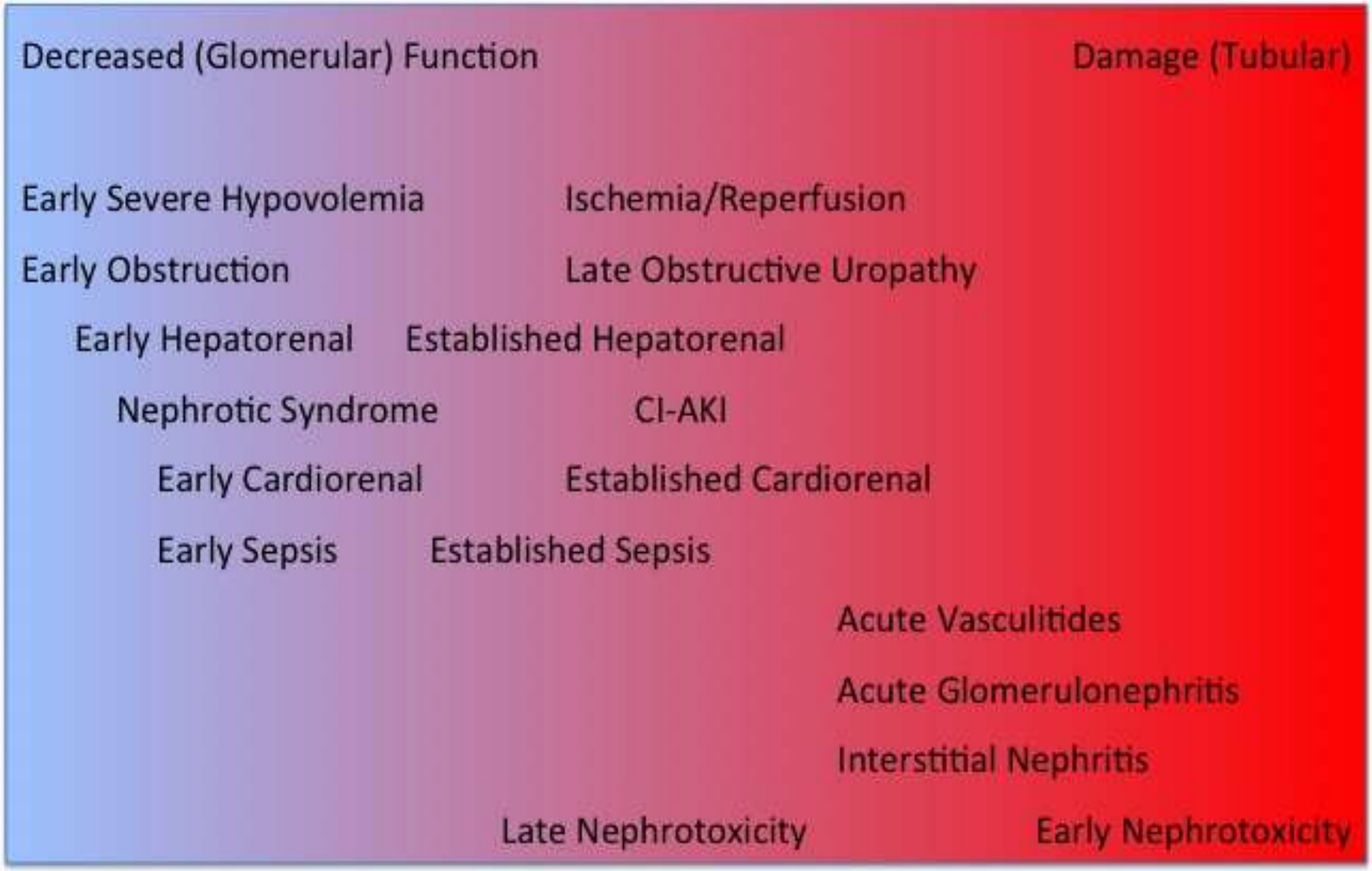


Sasaki et al. (2011). *Biomarkers*

Just Diagnosing AKI or Severity of AKI Does not allow us to individualise Treatment:

Biomarkers need to define injury at the time of intervention: Phase of Injury

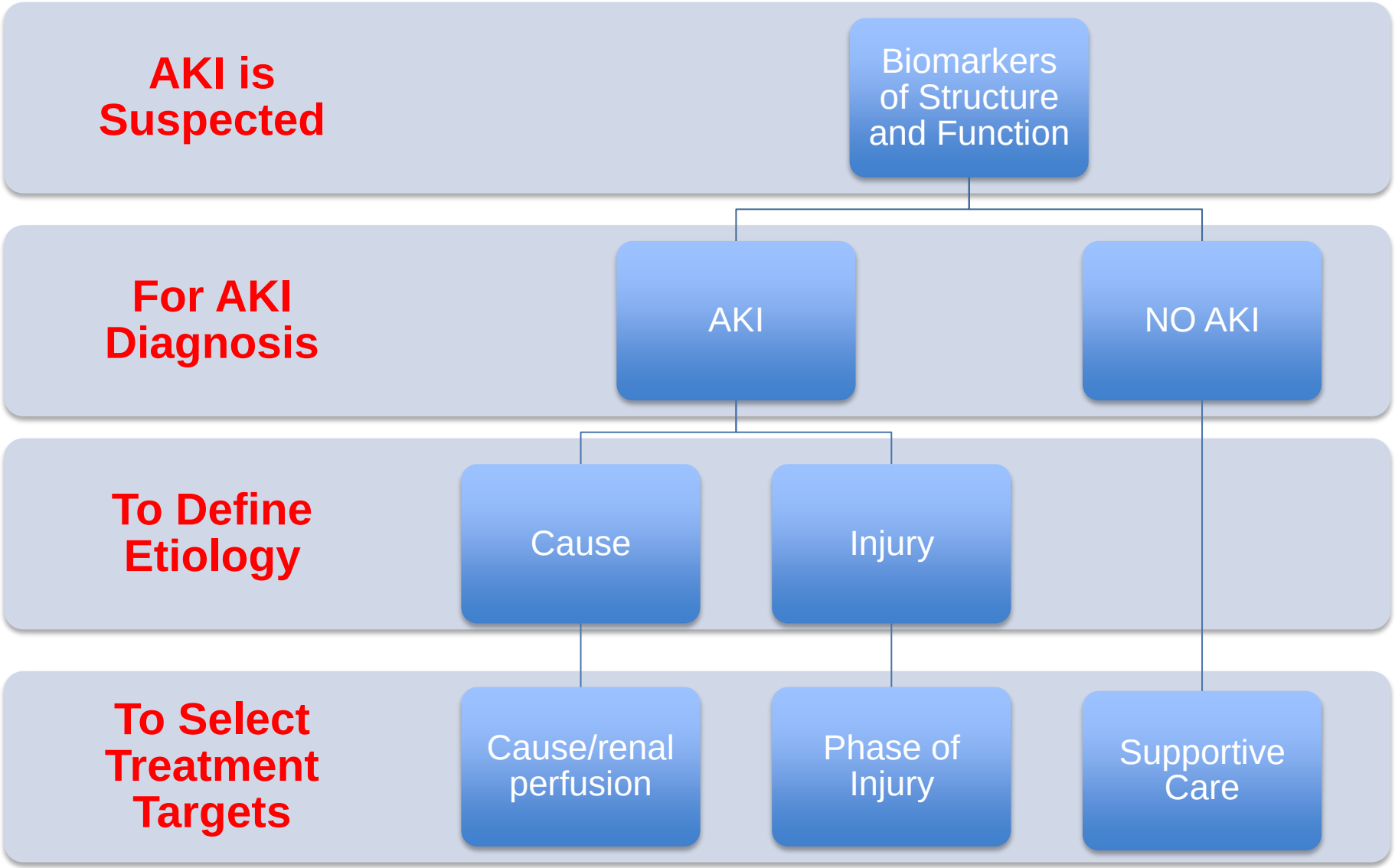
Biomarkers Differentiate Cause



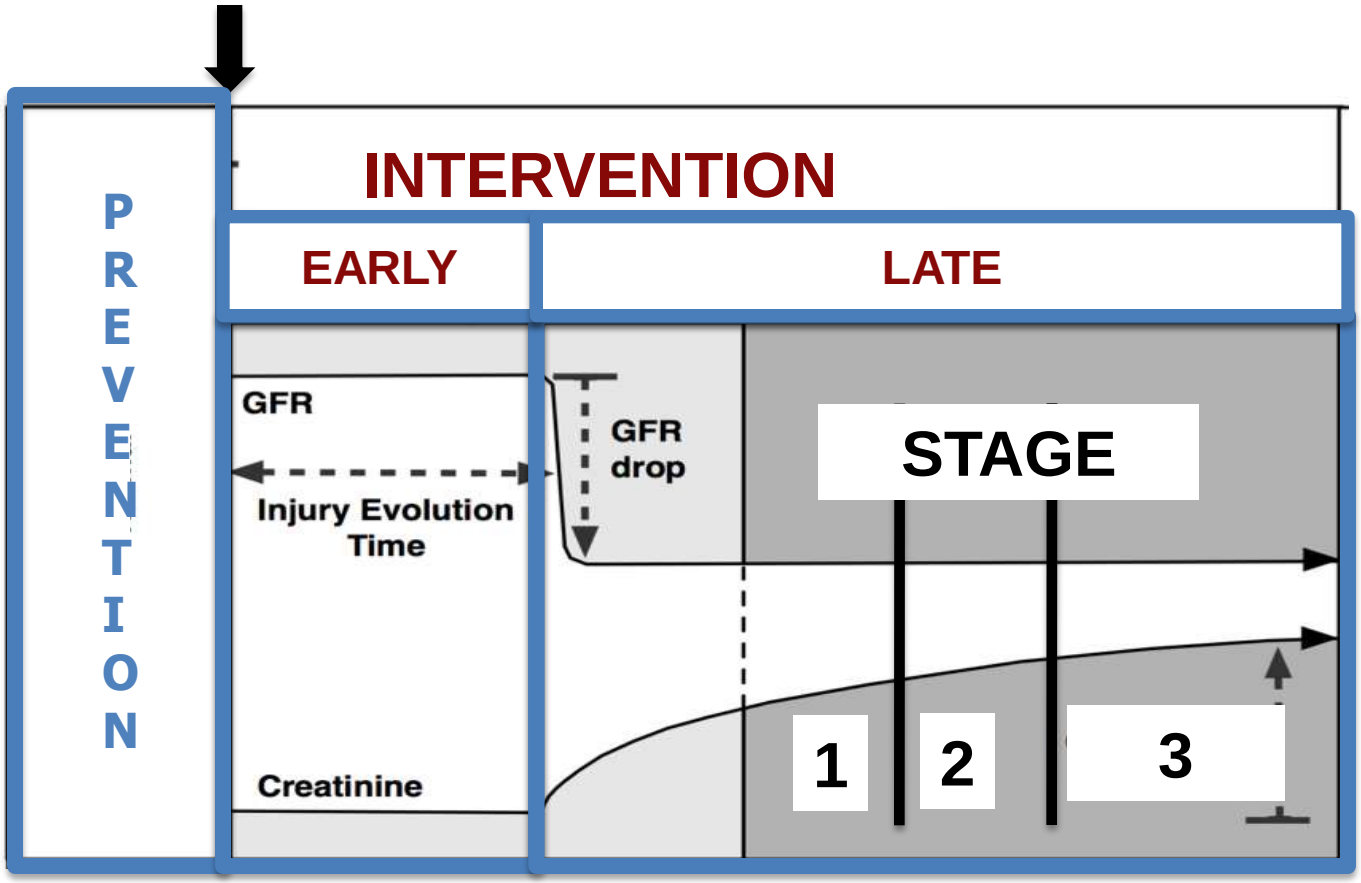
	NGAL	IL-18	KIM-1	CysC	L-FABP
Hypovolemic AKI	+/-	+/-	+/-	+/-	+/-
Sepsis	+	+/-	?	+	+
Post-CPB	+	+	+	+	+
Contrast-induced	+	+	+	+	+
Nephrotoxic	+	+	+	?	+
Renal Transplant – Delayed Graft Function	+	+	-	+	?

Cause Specific Biomarkers Depend on Clinical Context

At Risk Patient - Use Biomarkers When:



Phase vs Stage of AKI



PHAS

Vasoconstriction,
Leucostasis
Vascular Congestion

ATP Depletion

Apoptosis

Inflammation

De-differentiation

Proliferation

Biomarkers of Phase of Injury

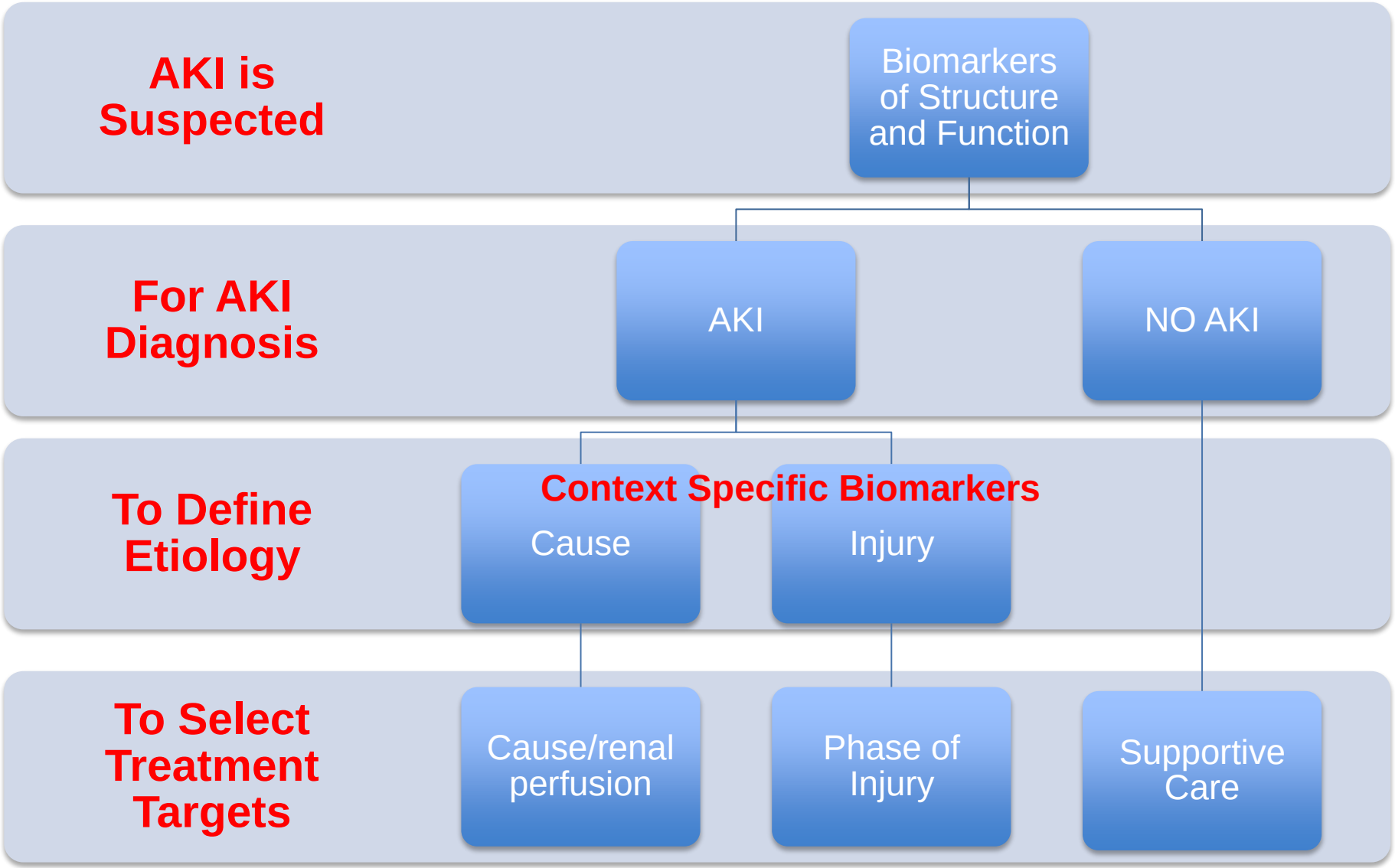
- **Initiation:**
- **Inflammation:**
- **Dedifferentiation:**
- **Regeneration:**
- **Recovery:**

- **Injury:** **Non-Specific**

Biomarkers of Phase of Injury

- **Initiation:** ?
- **Inflammation:** NGAL, TNF-a, IL-18, ?L-FABP
- **Dedifferentiation:** KIM-1
- **Regeneration:** RPA-1
- **Recovery:** KIM-1, CLU, OPN, LCN2, albumin, GSTα and TFF (serum cystatin C), osteopontin
- **"Injury":** All! incl: preformed (GGT, GST,NAG..), L-FABP, cystatin C, recruited (IL-18), etc…!

At Risk Patient - Use Biomarkers When:



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