Early detection of acute kidney injury

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What is AKI ?

- Acute kidney injury (AKI) is a common and devastating problem in clinical medicine. Previously known as acute renal failure (ARF).

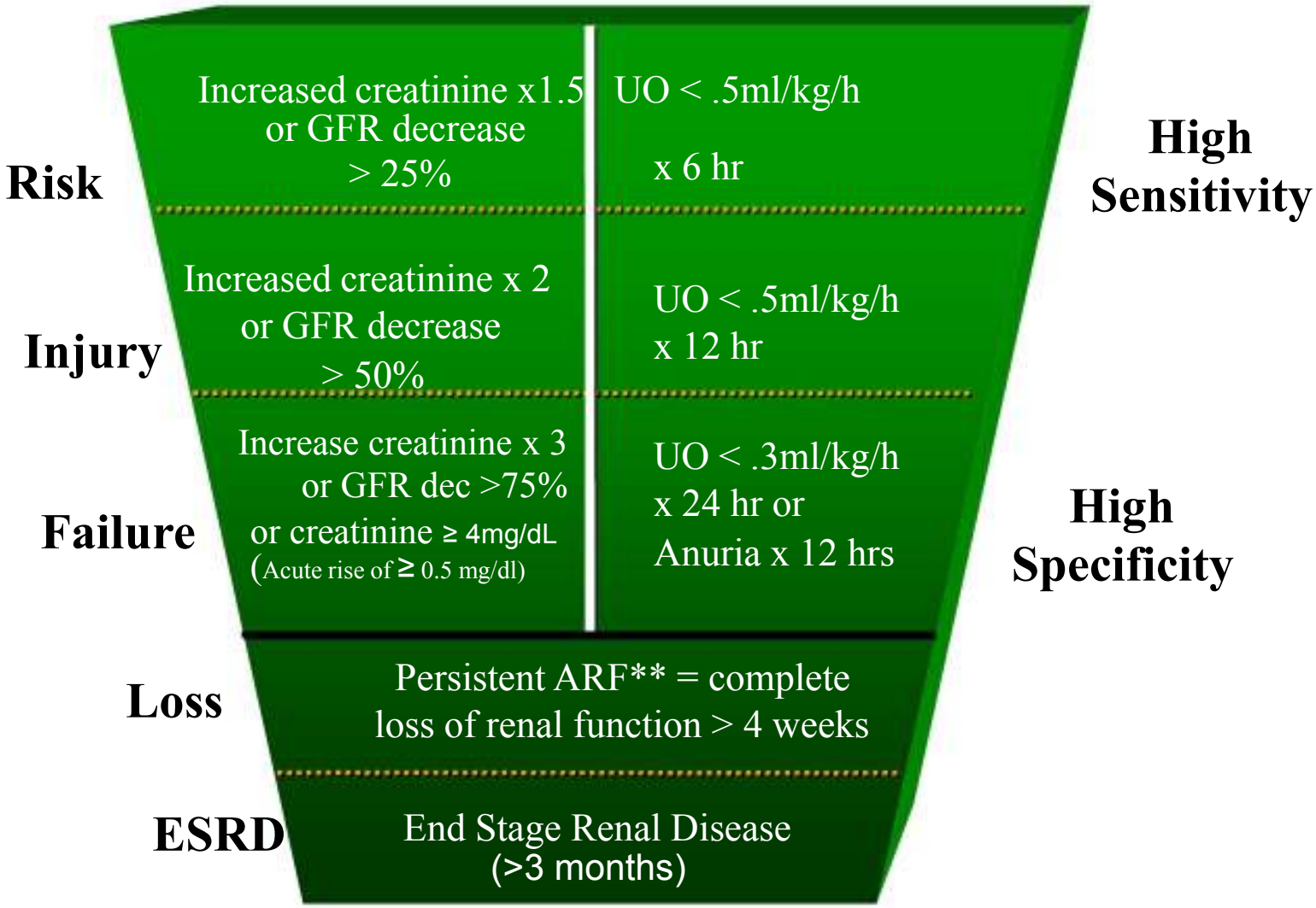
- Characterized by an abrupt (hours to days) decline in kidney function. Diagnosis usually based on either an elevation of serum creatinine and/or detection of decreased urine production (oliguria).

Definition

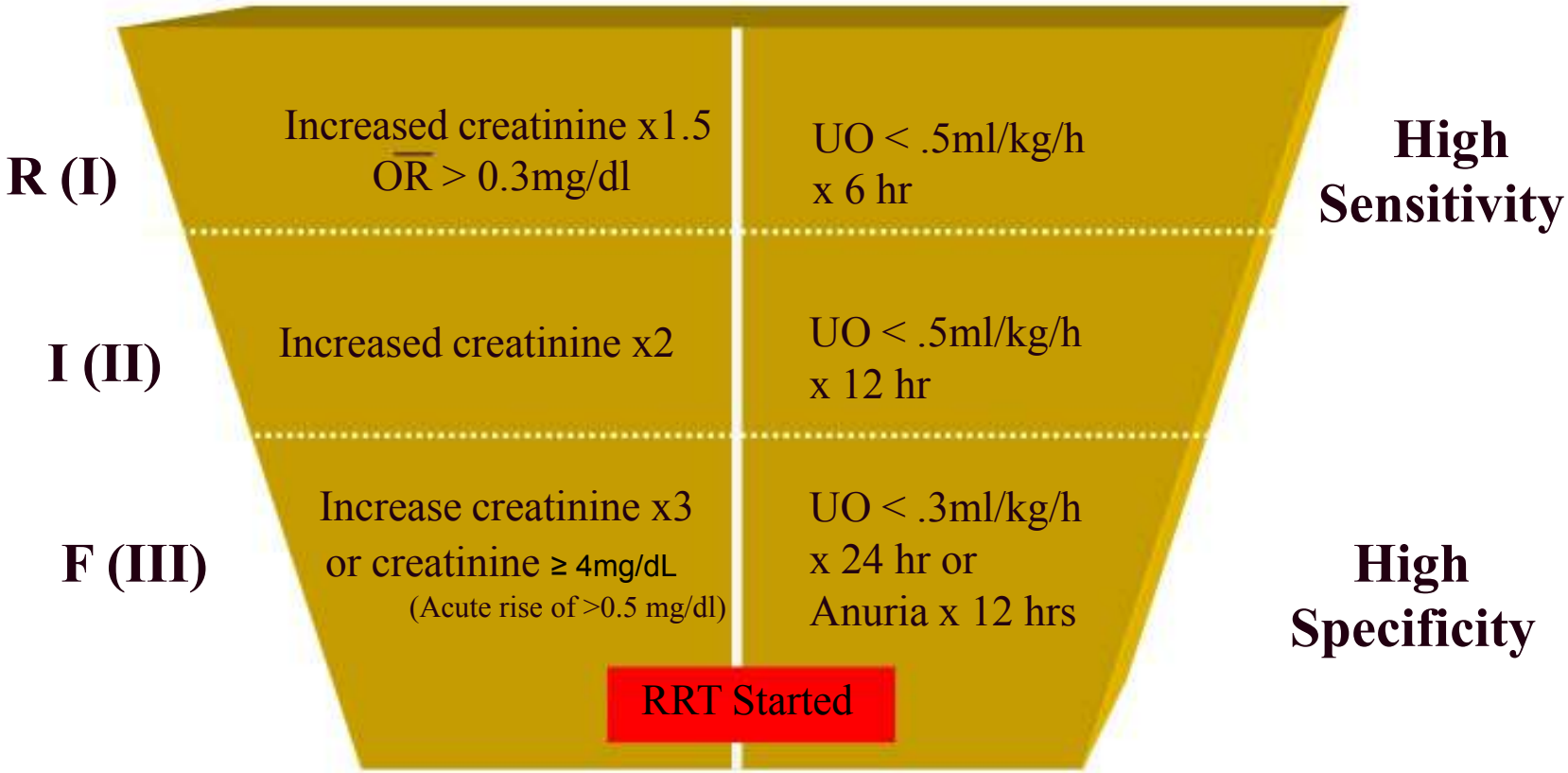
- Acute Kidney Injury Network (AKIN)
  - AKI - represent the entire spectrum of acute renal failure
- RIFLE Classification
  - three levels of injury (Risk, Injury, and Failure)
  - two outcome measures (Loss and ESRD)

Critical Care. 2007, **11(2)**:R31

RIFLE Criteria for Acute Renal Dysfunction



MODIFICATIONS PROPOSED BY AKIN



Diagnostic criteria for AKI

- abrupt (within 48 hours) absolute increase in the serum creatinine concentration of ≥0.3 mg/dL from baseline

or Increase in the serum creatinine ≥ 50 %

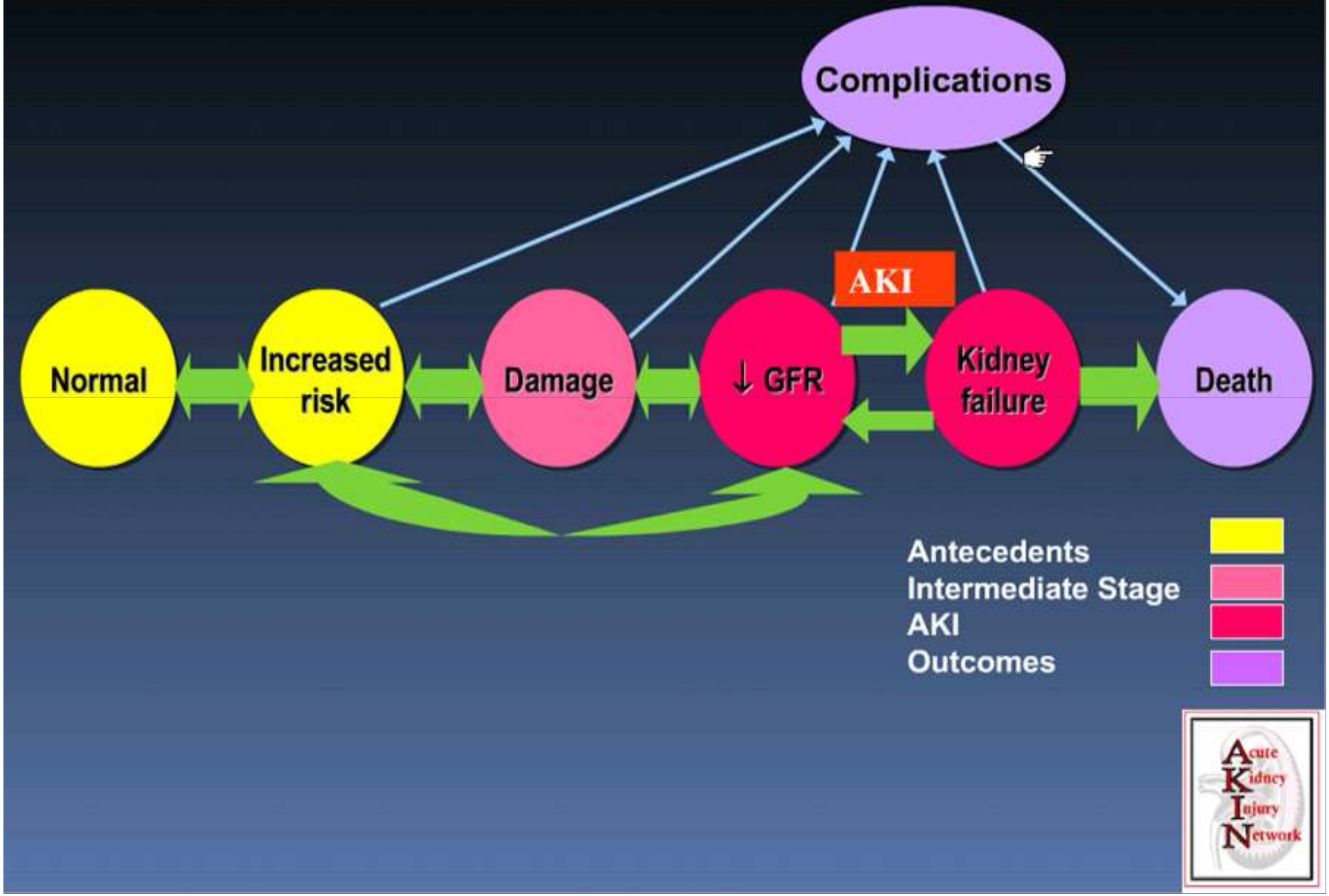
- Oliguria < 0.5 mL/kg per hour for > 6 hrs.

Critical Care. 2007, **11(2)**:R31

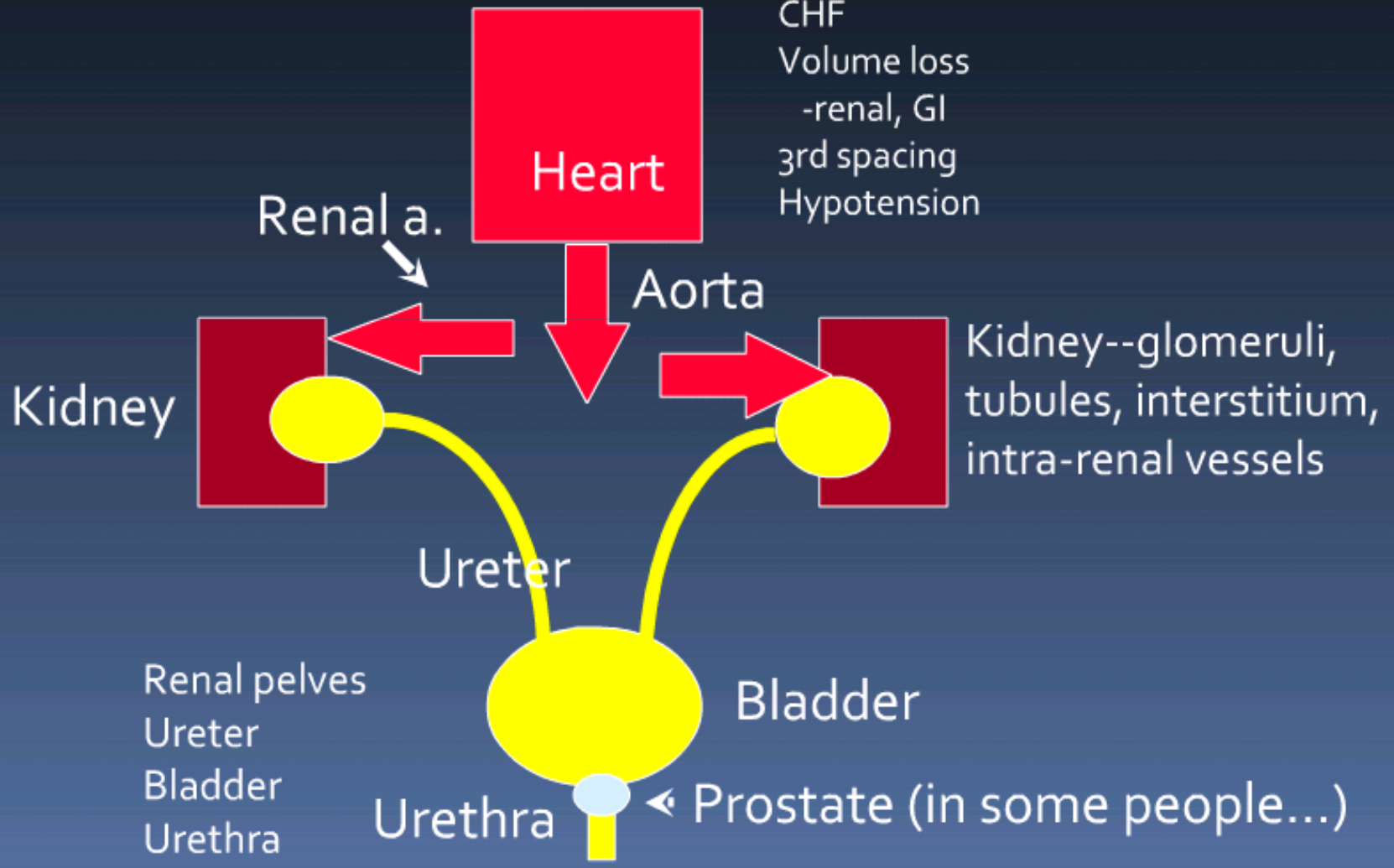
AKI-Epidemiology

- AKI is present in 5% of all hospitalized patients, and up to 50% of patients in ICUs
- The incidence is increasing – globally
- Mortality rate 50-80% in dialyzed ICU patients - 4 Million die each year of AKI
- AKI requiring dialysis is one of the most important independent predictors of death in ICU patients 25% of ICU dialysis survivors progress to ESRD within 3 years

Conceptual Model for AKI



Macroanatomy of AKI
The Black Box Approach

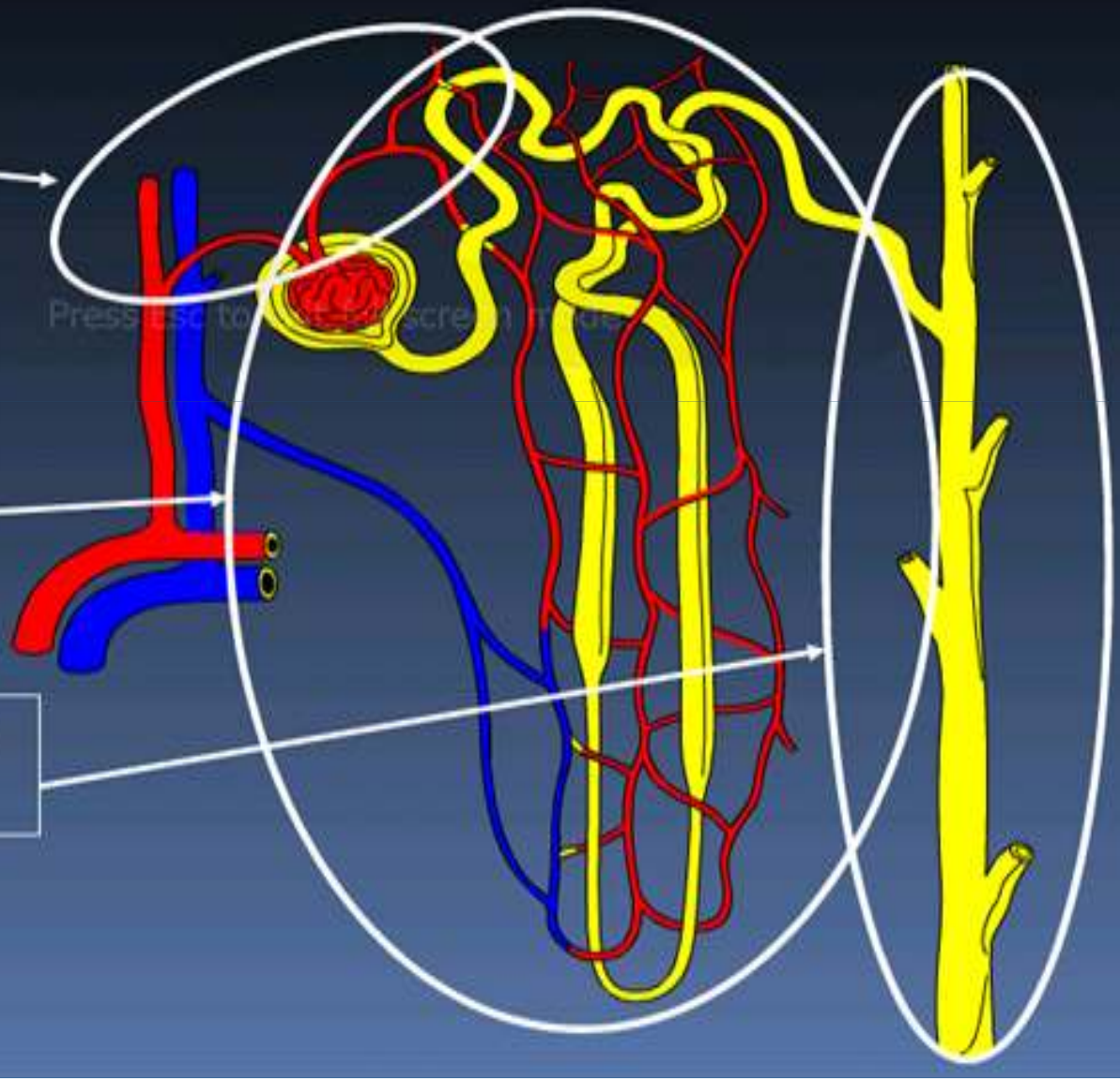


Microanatomy of Acute Kidney Injury

Pre-renal: decreased effective arterial blood volume and thus decreased renal blood flow

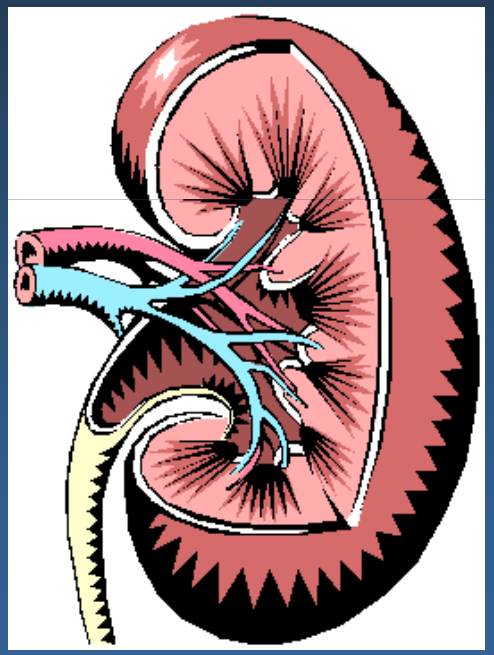
Intra-renal: intrinsic, parenchymal renal insult (glomerulus, tubules, interstitium, glomerular and peritubular capillaries)

Post-renal: obstruction of urine flow



Etiology

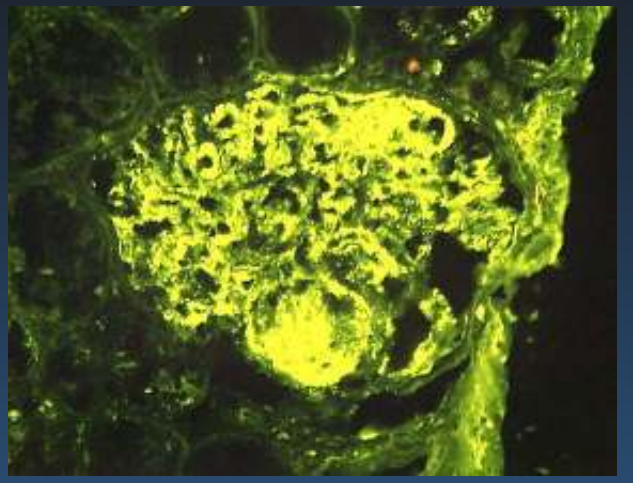
- **Prerenal (40-80% cases)**
  - Volume depletion
    - Blood loss: surgery, trauma, gastrointestinal or genitourinary bleeding
    - Gastrointestinal: vomiting, diarrhea
    - Urinary (diuretics, diabetes insipidus)
    - Cutaneous losses (burns, fever)
  - Decreased Arterial Blood Pressure
    - Low Cardiac output
    - Cardio renal syndrome type 1
    - Sepsis/shock
    - Hepatorenal syndrome
    - Drugs: ACEI, NSAIDS



Thadhani R. NEJM. 1996; 334:1448–1460

Etiology

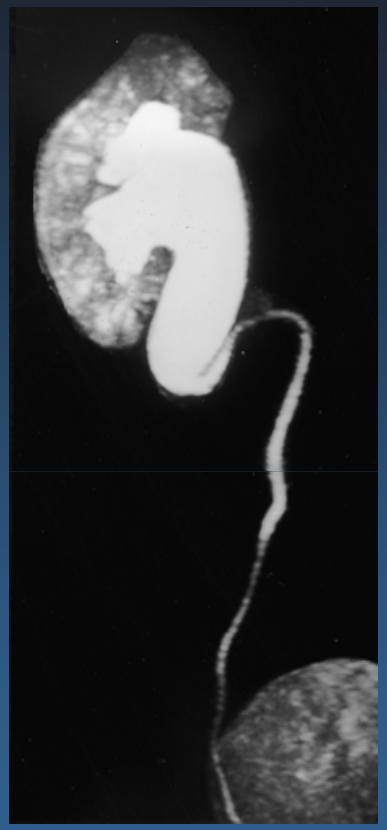
- Renal (5-15%)
  - Vascular
    - Thrombosis (arterial and venous)
    - Renal artery stenosis
    - Hemolytic-uraemic syndrome
    - Malignant hypertension
    - Vasculitis (Wegener's, SLE).
    - Scleroderma
  - Glomerular
    - Acute glomerulonephritis: vasculitis, post-infectious (Streptococcus).
  - Tubular and interstitial disease
    - Acute tubular necrosis (ATN) – ischemia or injury from tubular nephrotoxins
    - Nephrotoxic agents: aminoglycosides, amphotericin B, contrast agents
    - Rhabdomyolysis
    - Tumor lysis syndrome
    - Acute interstitial nephritis – Eosinophiluria, drug hypersensitivity
    - Nephrolithiasis



Thadhani R. NEJM. 1996; 334:1448–1460

Etiology

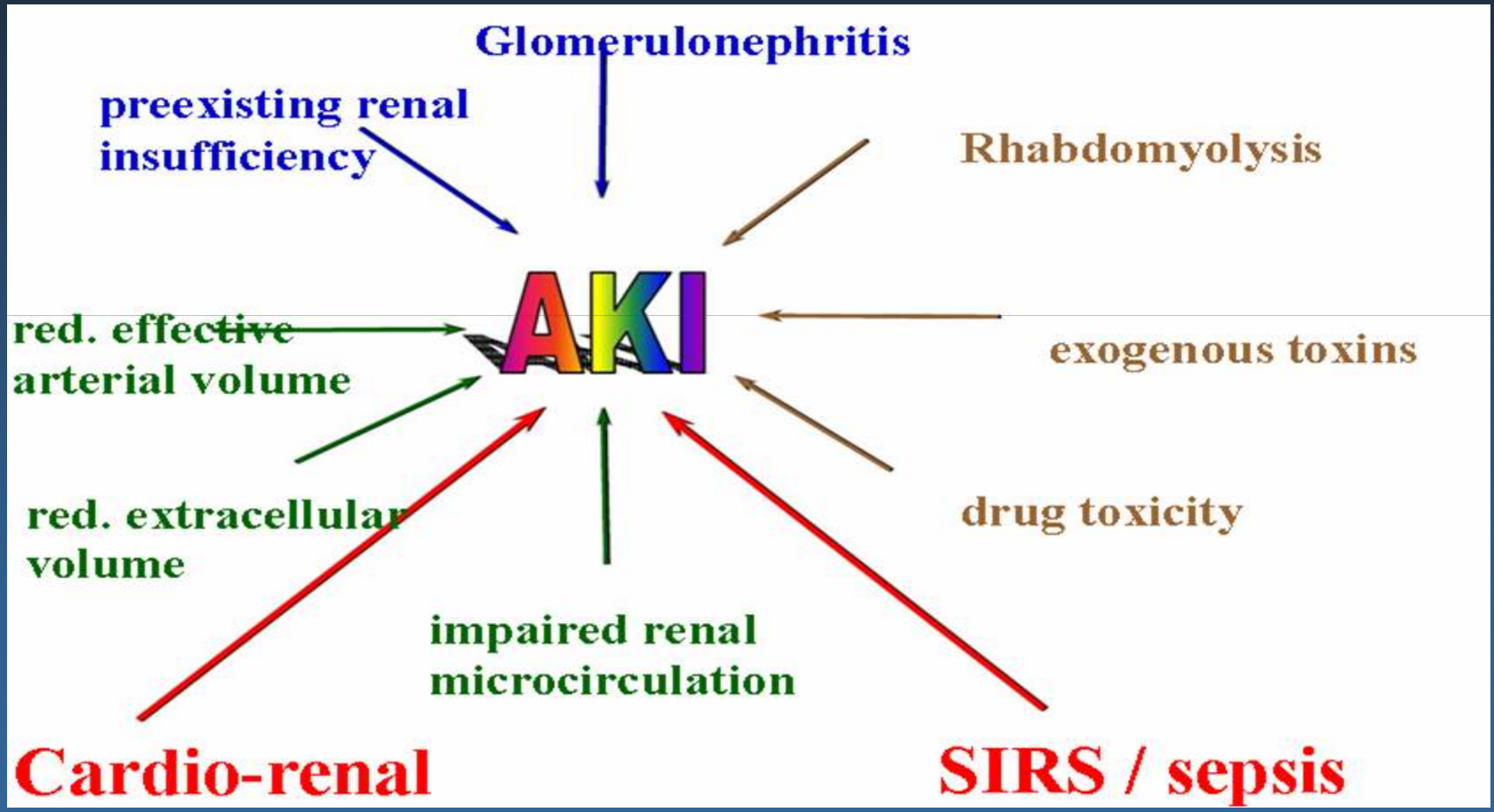
- **Postrenal** (10-30%)
  - Bilateral urinary tract obstruction
    - PUV (children)
    - BPH
    - Retroperitoneal malignancies
    - Urethral strictures
    - Nephrolithiasis
    - Catheters
    - Neurogenic bladder



Thadhani R. NEJM. 1996; 334:1448–1460

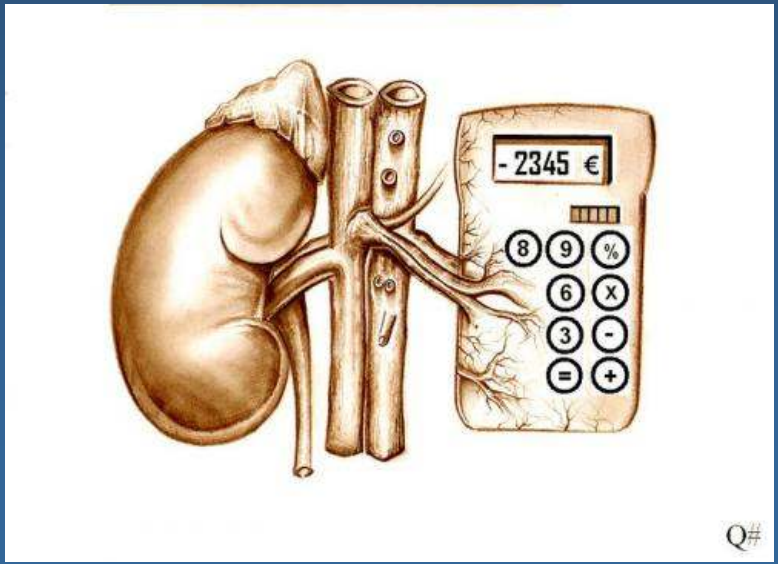
British Journal of Radiology.2002;75:177-179

Etiology


Glomerulonephritis
preexisting renal insufficiency
Rhabdomyolysis
AKI
red. effective arterial volume
exogenous toxins
red. extracellular volume
drug toxicity
impaired renal microcirculation
Cardio-renal
SIRS / sepsis

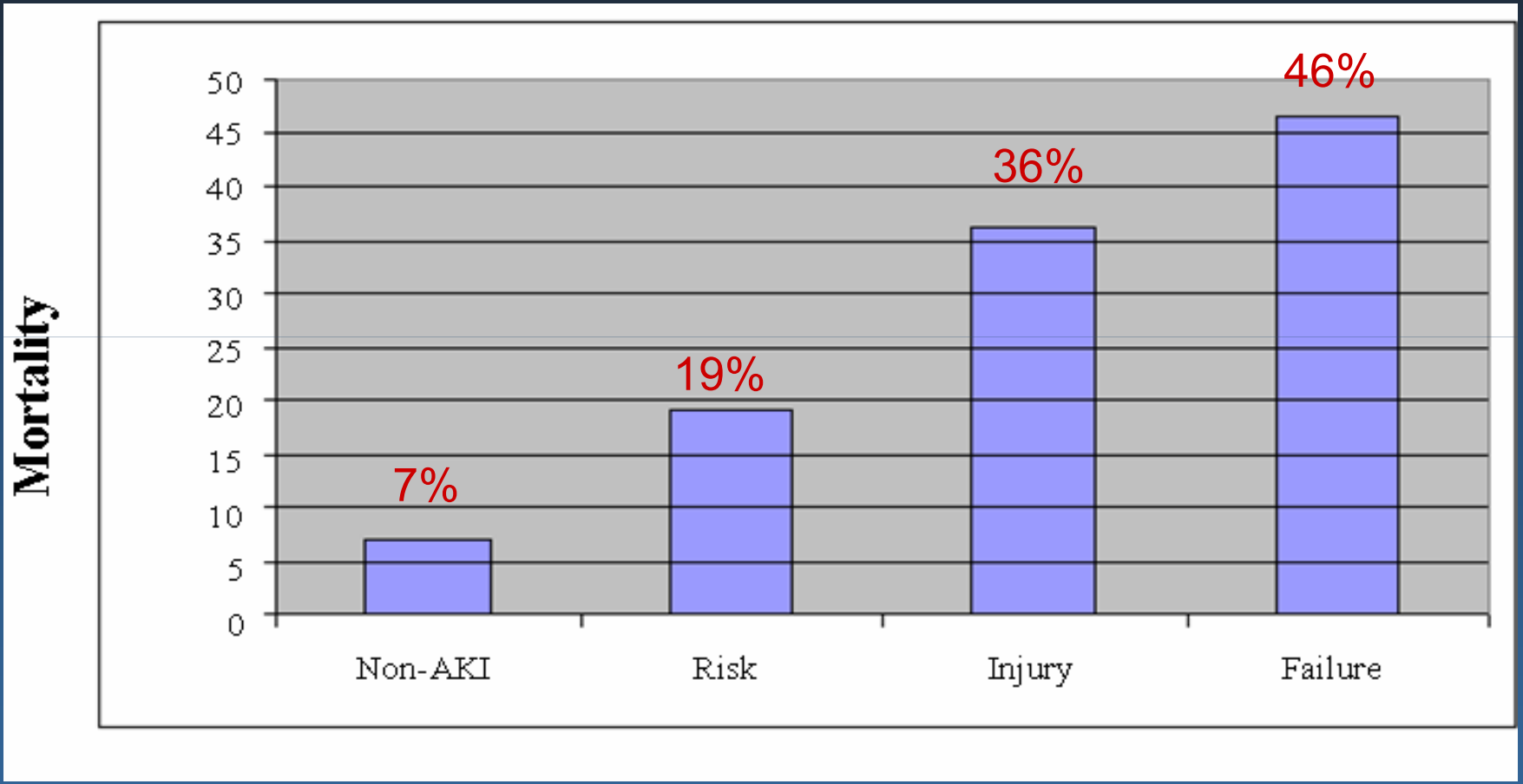
Economic burden of AKI

"As a conservative estimate, roughly 17 million hospital admissions annually in the United States are complicated by AKI, resulting in **over $10 billion** in costs to the healthcare system".



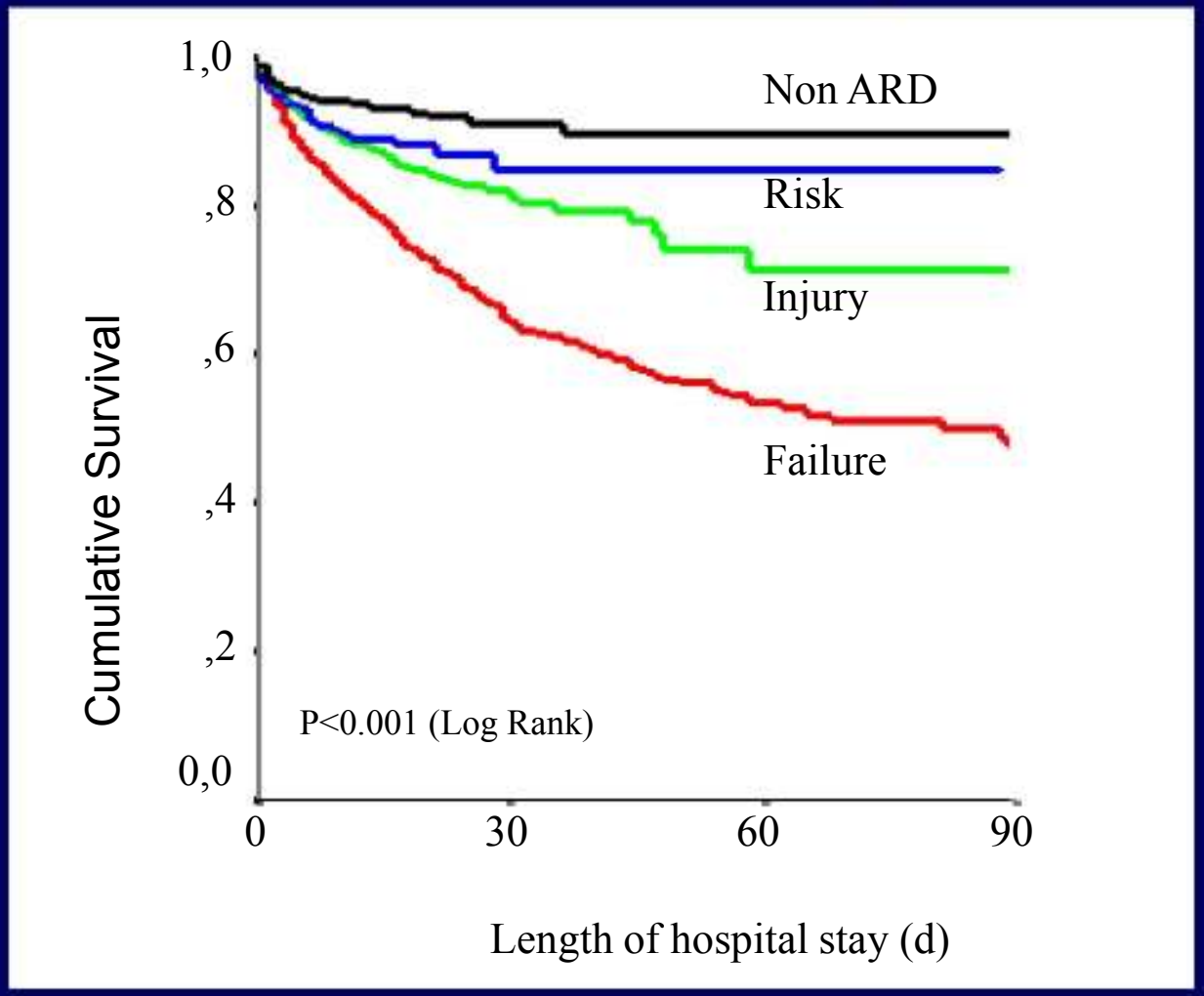
Parikh, et al. Arch Intern Med 2008
Chertow, et al. J am Soc Nephrol 2005

Mortality by RIFLE class



RIFLE max

Early Detection is Good!



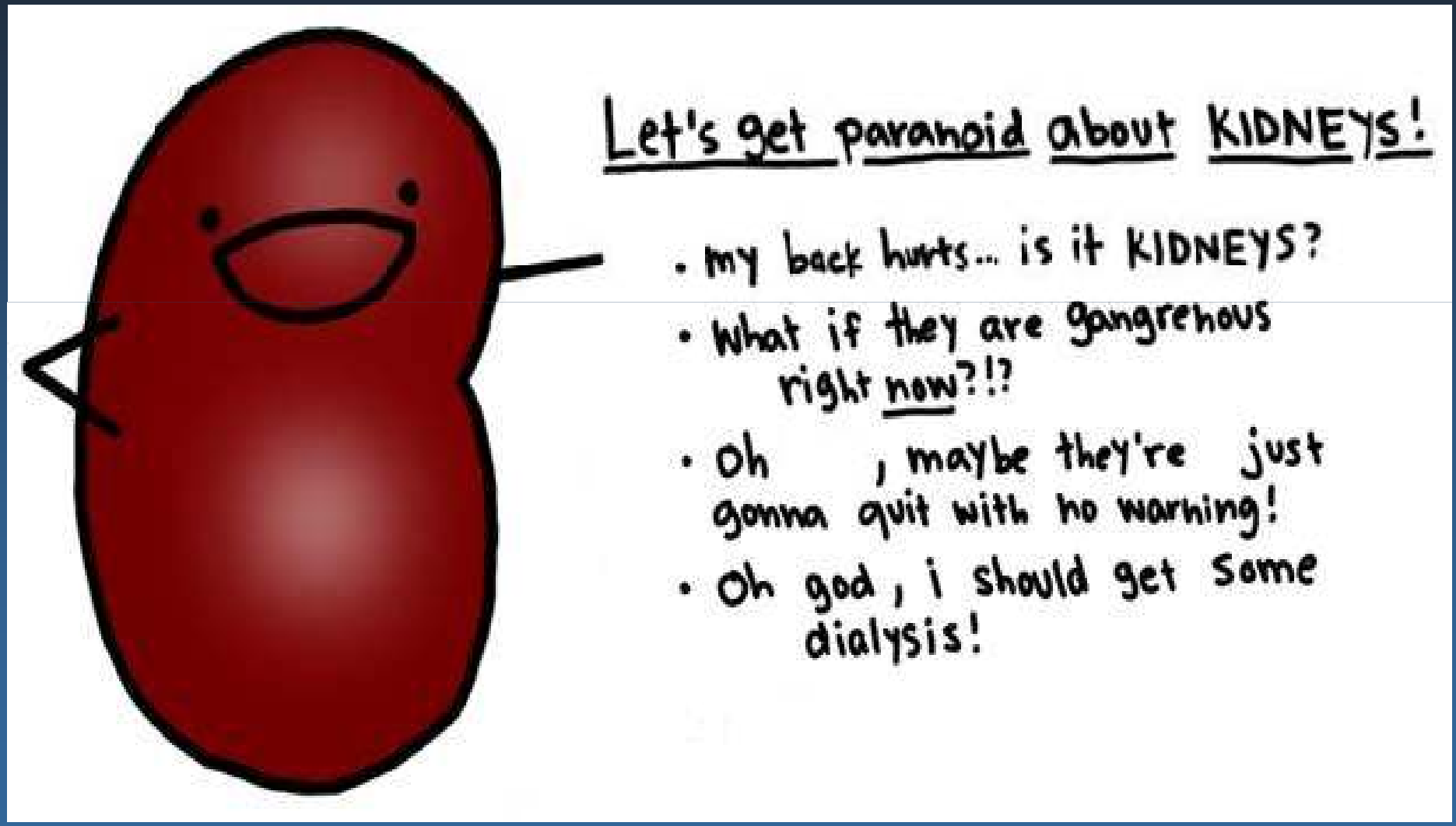
Hospital acquired AKI – mortality and cost associated with increasing serum creatinine

Increase in sCr	Mortality (odds ratio)*	AUC+	Increase in total cost per patient (USD)
0.3 mg/dL (26.2 umol/L)	4.1 (3.1 – 5.5)	0.84	$4,886
0.5 mg/dL (44 umol/L)	6.5 (5.0 – 8.5)	0.86	$7,499
1.0 mg/dL (88.4 umol/L)	9.7 (7.1 – 13.2)	0.84	$13,200
2.0 mg/dL (177 umol/L)	16.4 (10.3 – 26)	0.83	$22,023

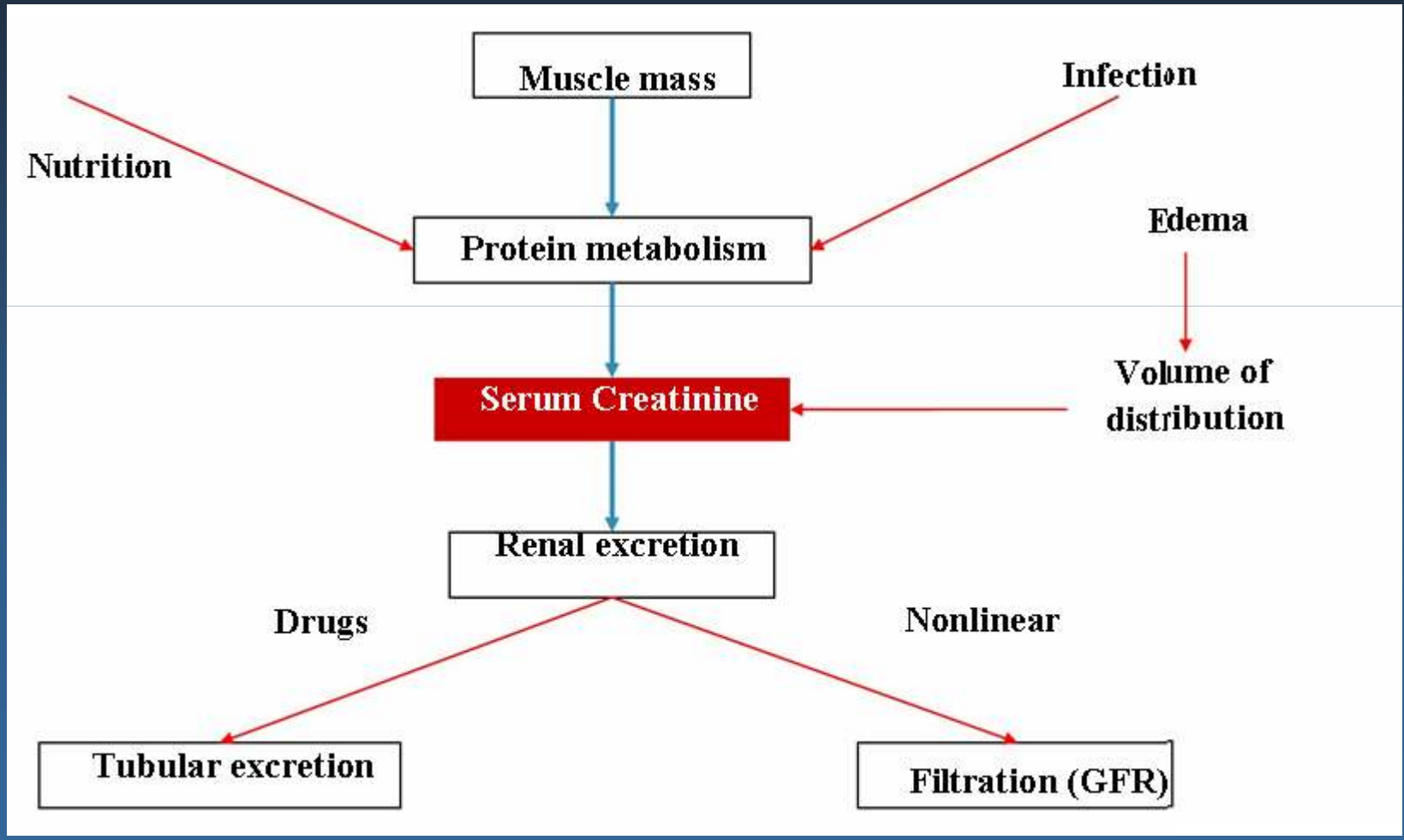
Traditional diagnostic investigations for AKI

- Serum and Urine chemistries/ indices
- Urinary sediments/ Casts
- Blood CP
- Serologies
- Toxicology Studies
- Radiological investigations

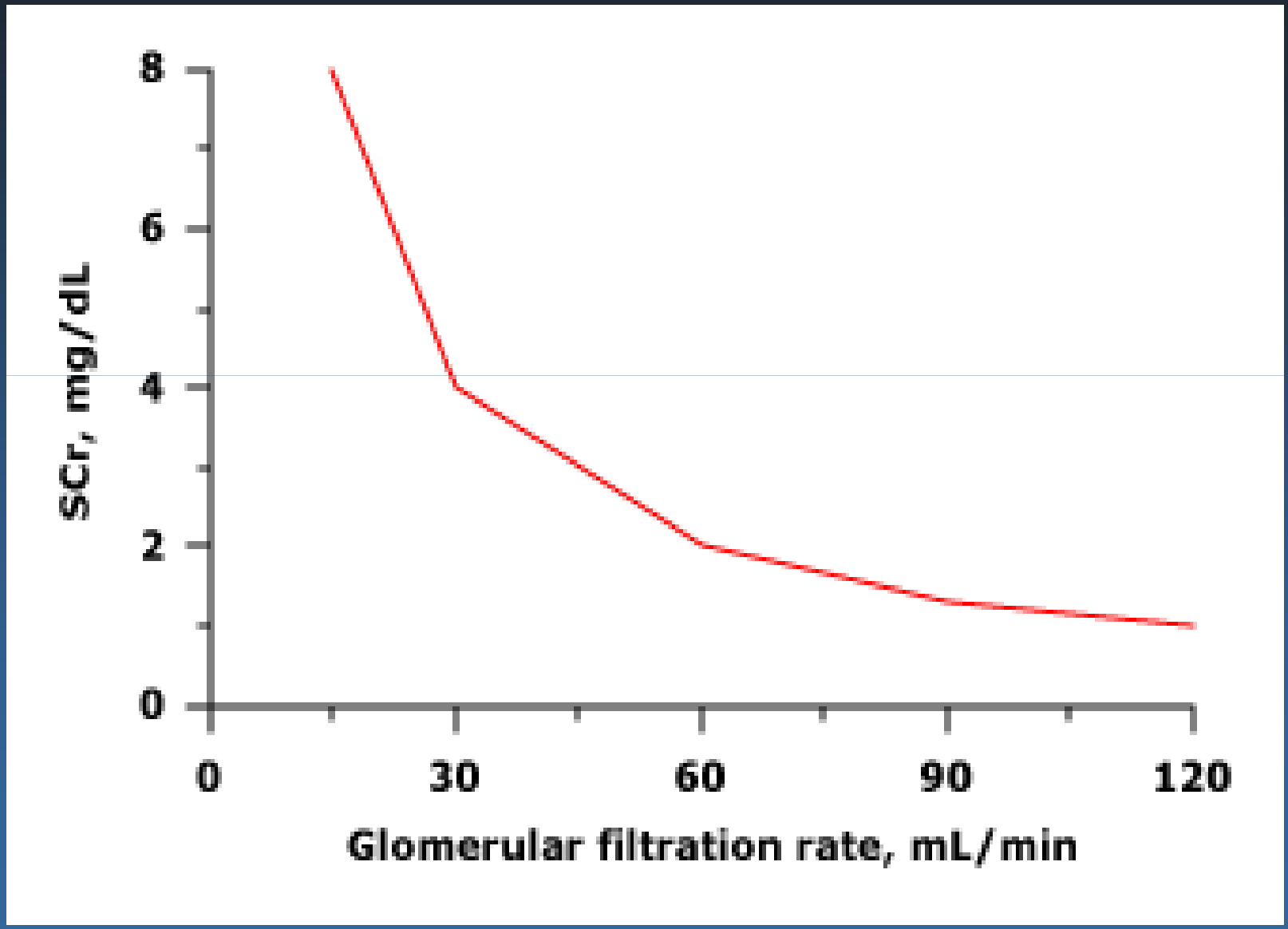
The dilemma of AKI diagnosis



Serum Creatinine and GFR in AKI



Serum Creatinine and GFR



Estimation equations

- MDRD

  eGFR= 186 x $Screat^{-1.154}$ X $Age^{-0.203}$ X 1.21 [if black] X o.74 [if female]

  Underestimates GFR in healthy people (when GFR >60 ml/min)

- Cockcroft-Gault formula

  (140-Age) X Mass (In KG) X [o.85 if female]/72 X Serum Creat

- **The non-steady-state conditions that prevail in ARF preclude estimation of GFR using standard formulae derived from patients with chronic kidney disease.**

The failure of creatinine as a marker for AKI

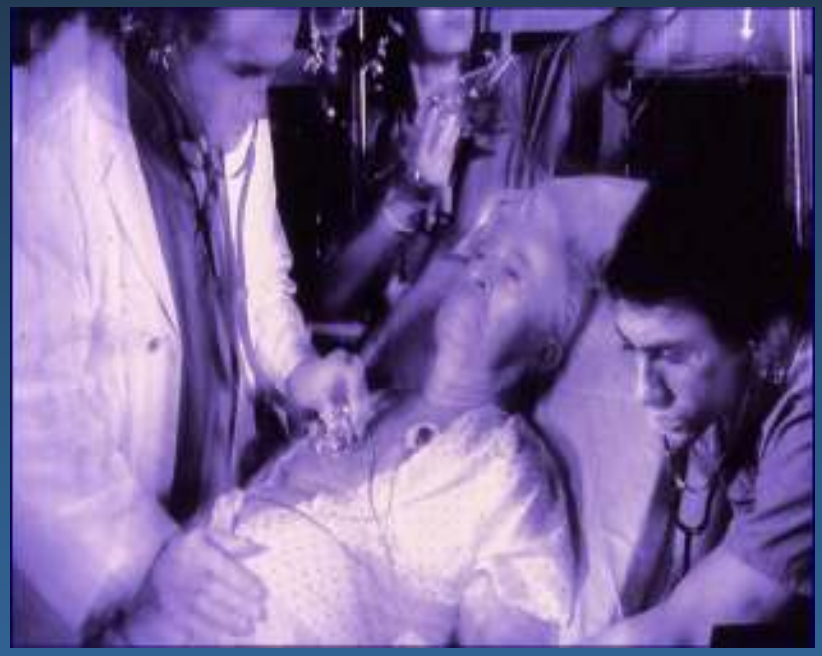
"Utilizing serum creatinine measurements to institute promising interventions for AKI in humans is futile, and analogous to waiting 2 – 3 days before intervening in patients with ischemic acute myocardial infarction or acute neurologic stroke."

"… the diagnosis, treatment, and prognosis of AKI have not changed appreciably in the last five decades."

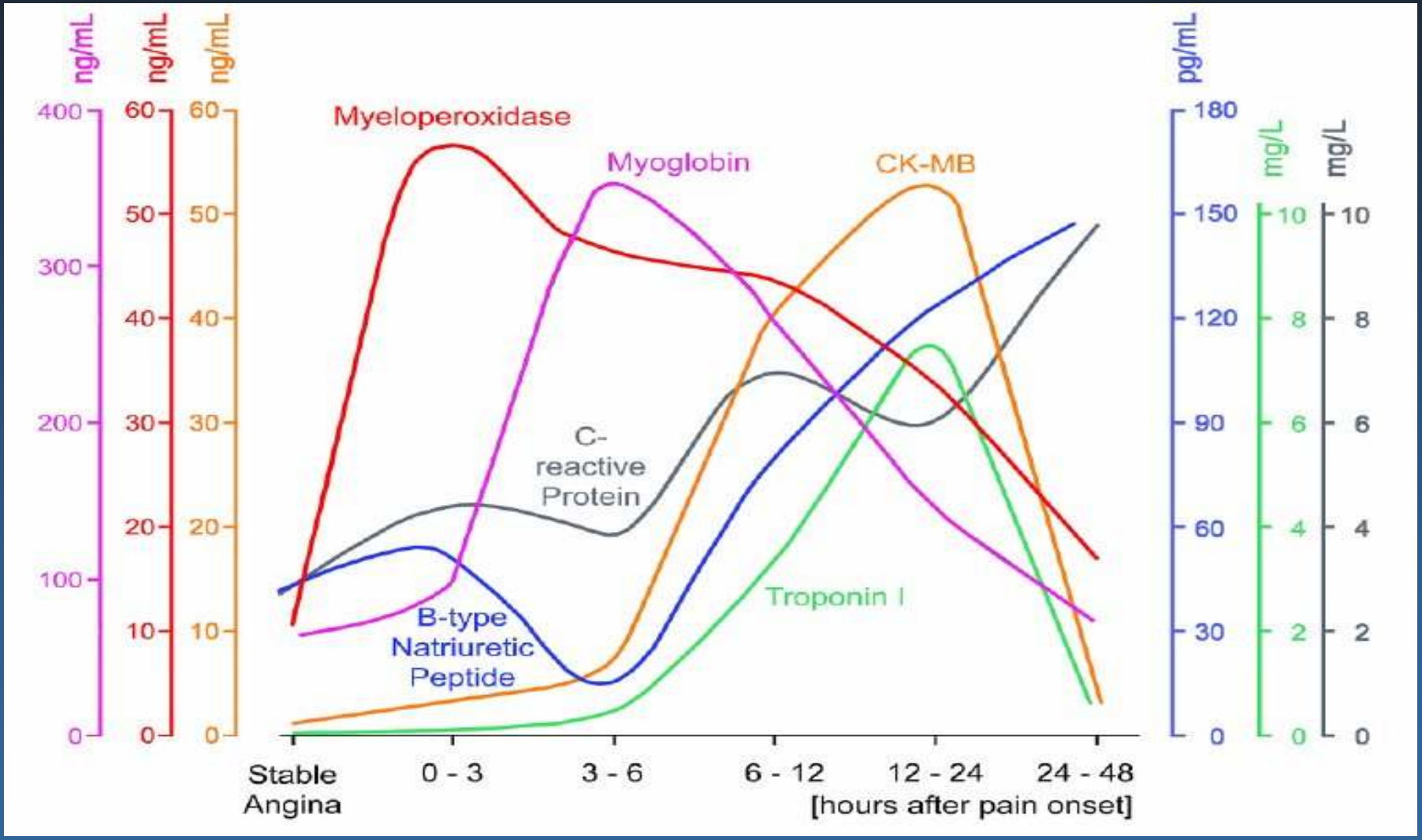
Devarajan, Expert Opin Med Diag 2008
Coca, etl al. Kid Internat 2007

AKI: urgent need for early diagnosis

- Early forms of AKI often reversible
- Early diagnosis may enable timely therapy narrow window of opportunity
- Paucity of early biomarkers has impaired ability to institute timely therapy in humans



ACS panel: a sharp contrast



Timecourse of Biomarker Elevation in ACS

Renal testing opportunity – begging for a change

YEAR	EVOLUTION IN DIAGNOSIS OF AMI	EVOLUTION IN DIAGNOSIS OF AKI
1950's	WBC count	Change in serum creatinine
1960's	LDH	
1970's	CPK	
1980's	CK-MB	
1990's	Troponin-T	
2000's	Troponin-I	
2010's	hrs CRP, MPO, BNP	Change in serum creatinine

The renal testing area is ripe for the introduction of novel, earlier and more specific biomarkers.

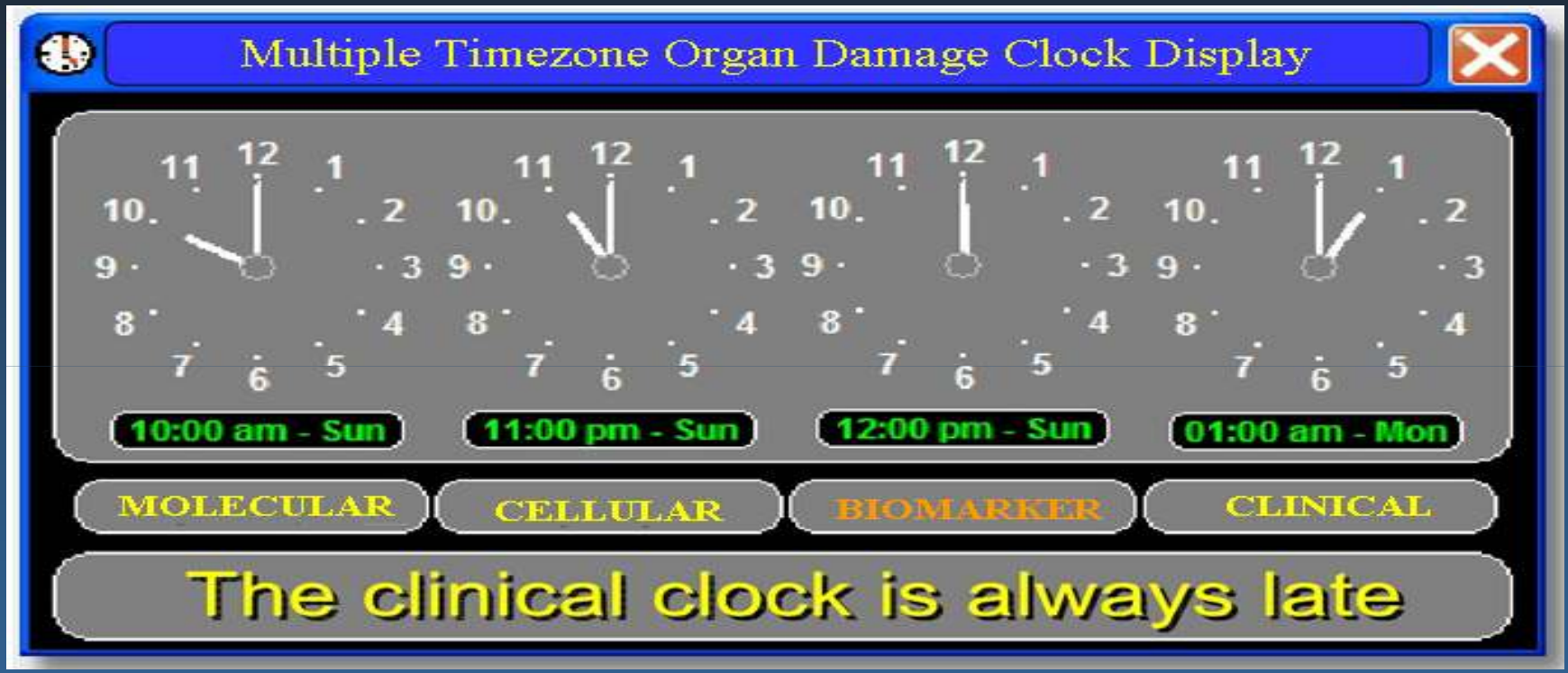
Better markers are needed for AKI

"A troponin like biomarker of AKI that is easily measured, unaffected by other biological variables, and capable of both early detection and risk stratification would substantially assist the diagnosis of AKI."

Devarajan, Expert Opin Med Diag 2008

Coca, etl al. Kid Internat 2007

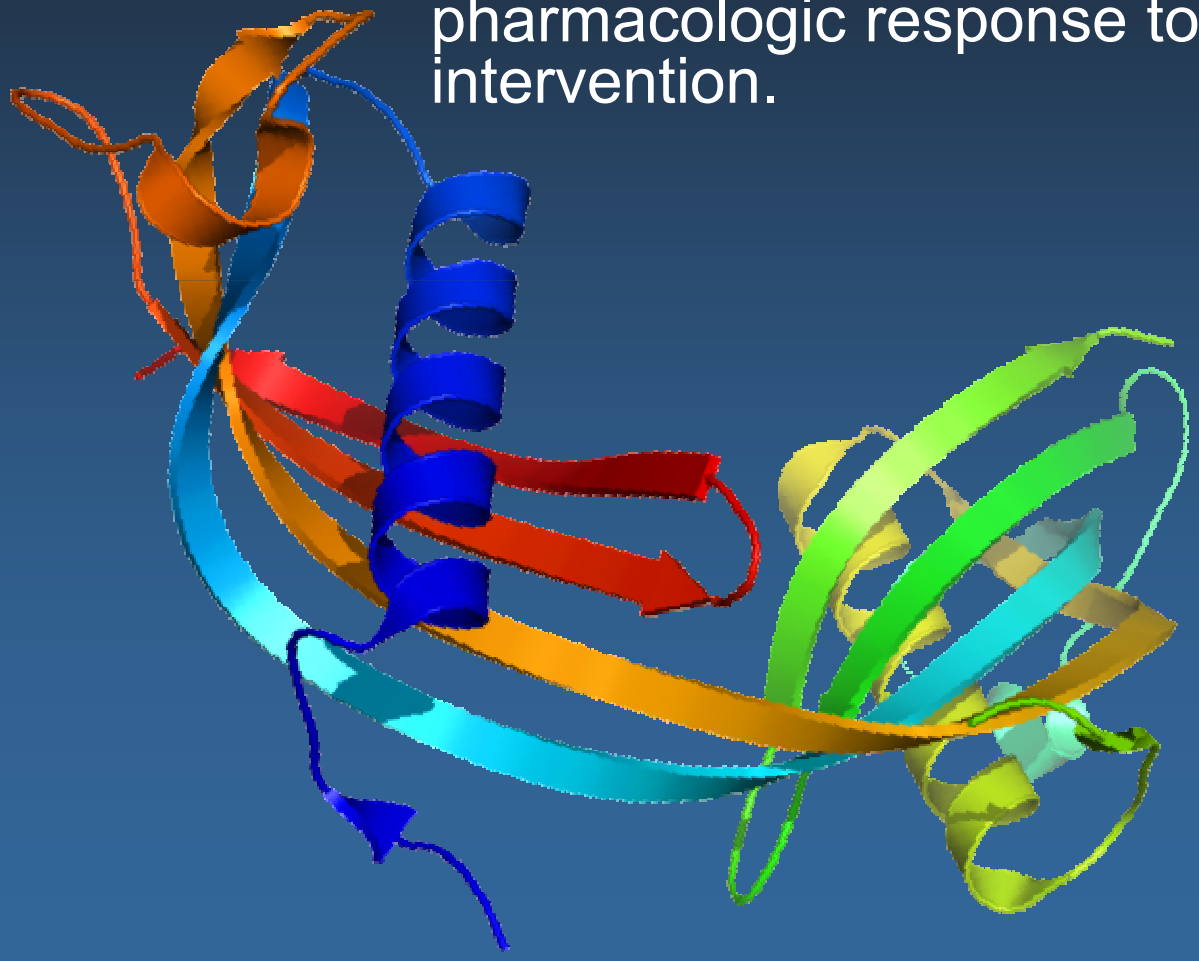
Analyze biology by time-zones with adequate and precision clocks



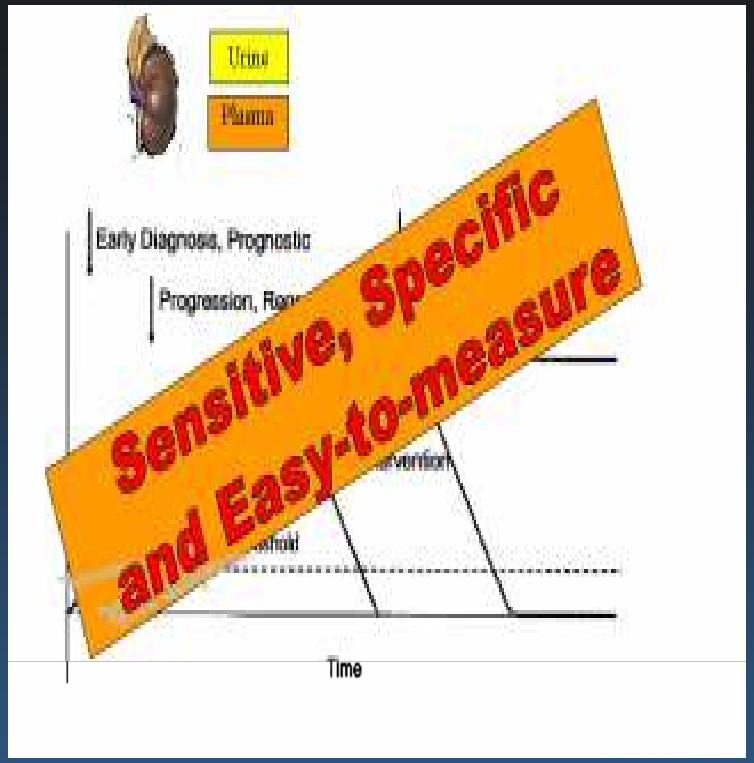
we can identify different milestones along the timeline of AKI. Injury begins inducing molecular modifications subsequently evolving into cellular damage. Cells start to produce biomarkers of injury and only later does the clinical picture of the syndrome develop with the typical sign and symptoms.

Biomarkers

A biomarker is a biological compound, objectively measurable, evaluated as an indicator of normal/pathological biological processes, or pharmacologic response to therapeutic intervention.



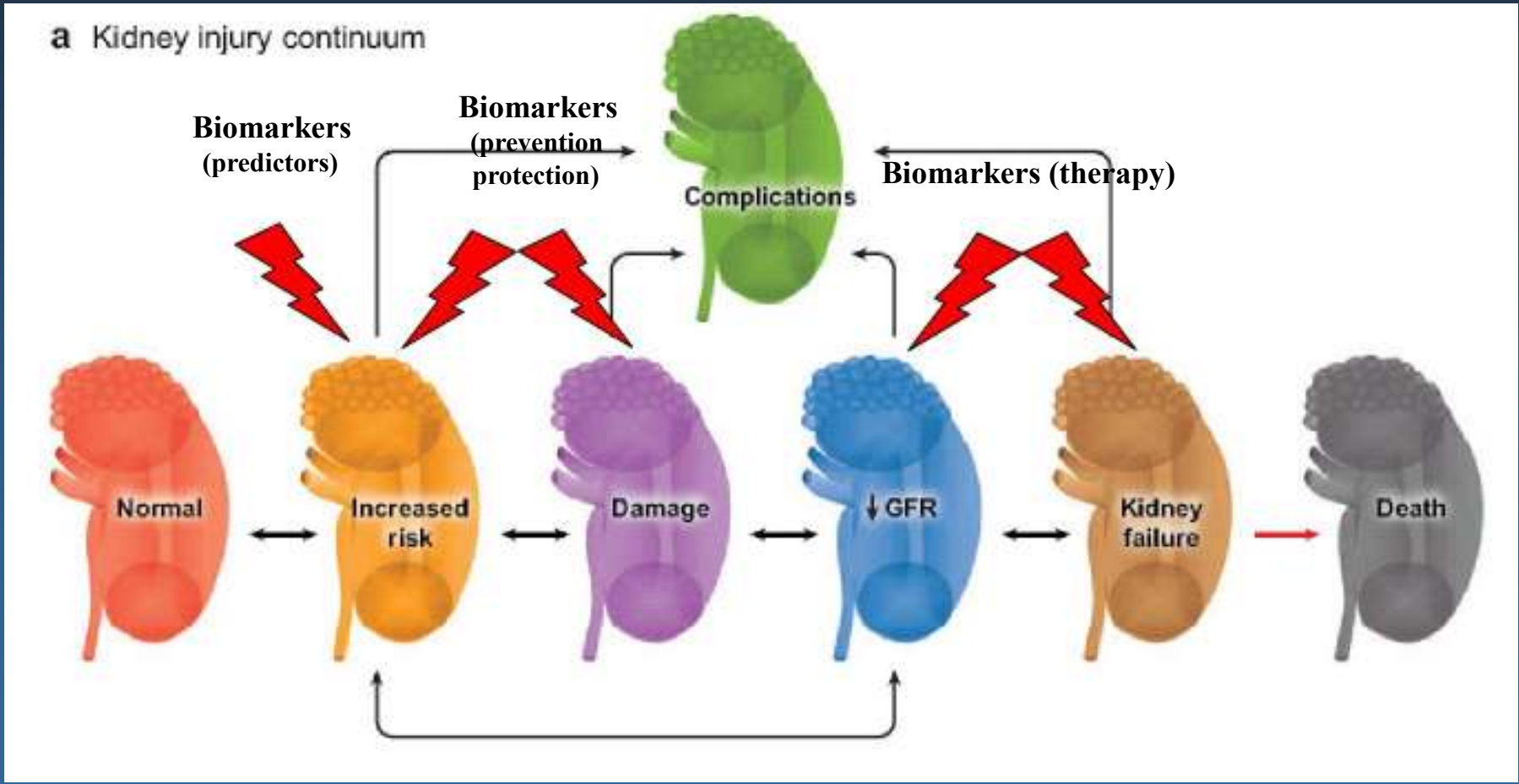
We need Biomarkers that are:



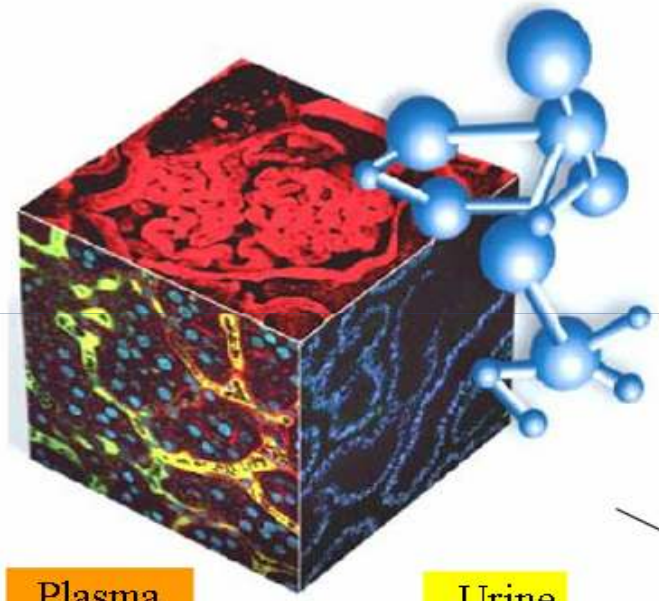
- Sensitive (early appearance)
- Easy to detect (diagnosis)
- Specific (typical of organ injury)
- Correlate with severity (prognosis)
- Identify etiologies (ischaemia, toxic)
- Quantitatively describing the level of injury even in the absence of typical clinical signs
- Monitoring response to injury
- Capable to indicate treatment initiation (theragnostics)

Conceptual model for AKI kidney injury continuum

Vaidya VS, Ferguson MA, Bonventre JV. Biomarkers of Acute Kidney Injury. Annu Rev Pharmacol Toxicol 2008;48:463-493



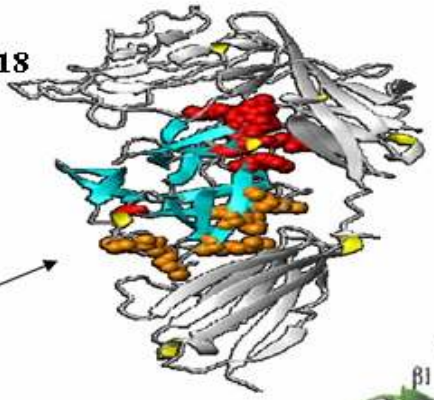
Biomarkers



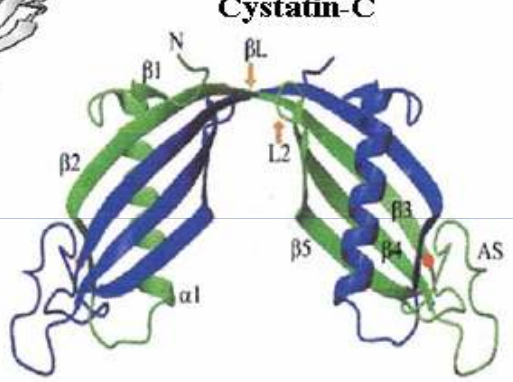
Plasma

Urine

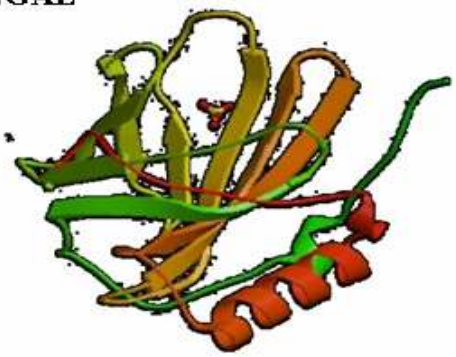
IL-18



Cystatin-C



NGAL

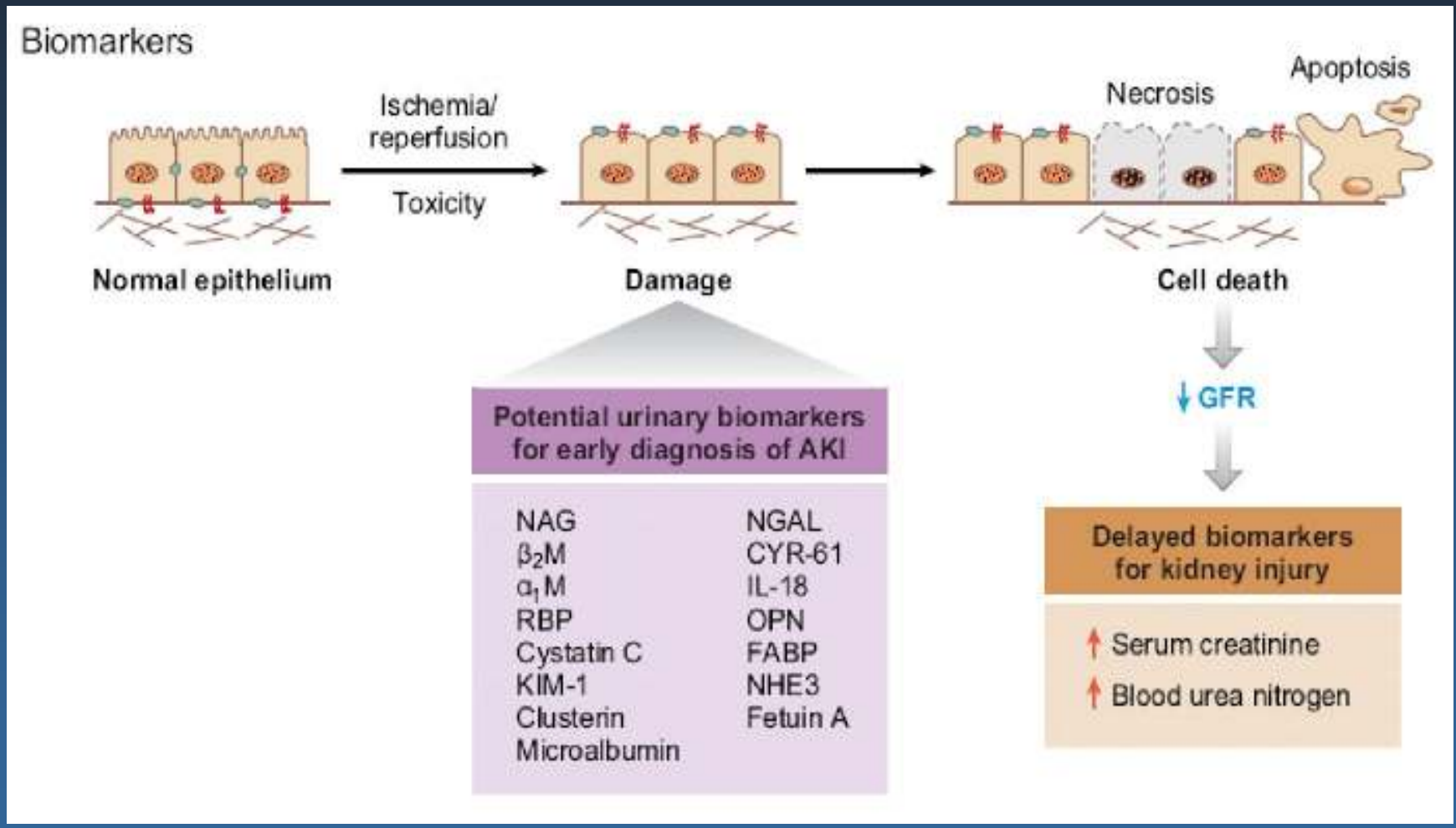


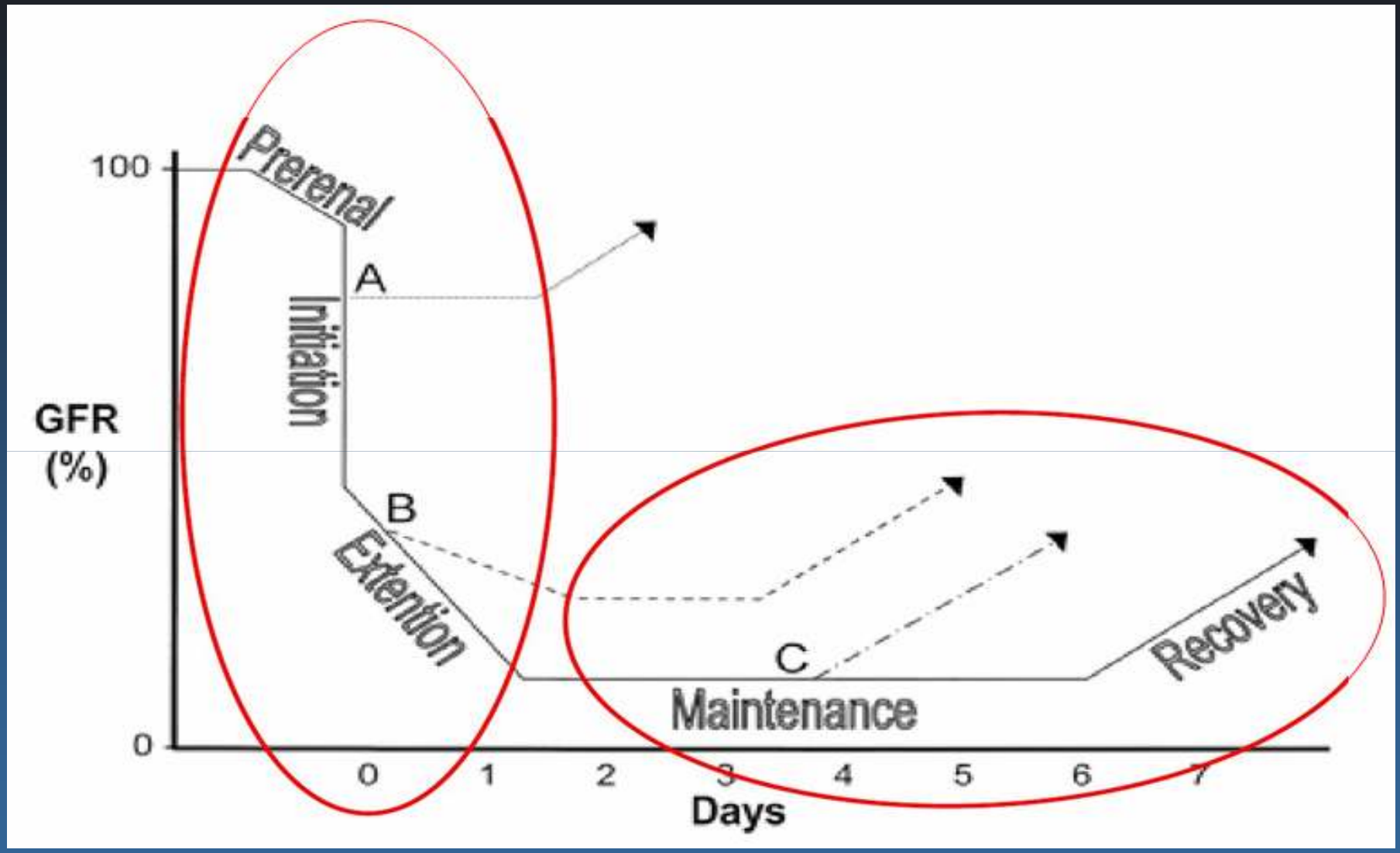
Using cDNA microarray as a screening technique, a subset of genes whose expression is up-regulated within the first few hours after renal injury can be discovered. (Or early GFR)

Acute kidney injury biomarkers

ANNU REV PHARMACOL TOXICOL 2008;48:463-493

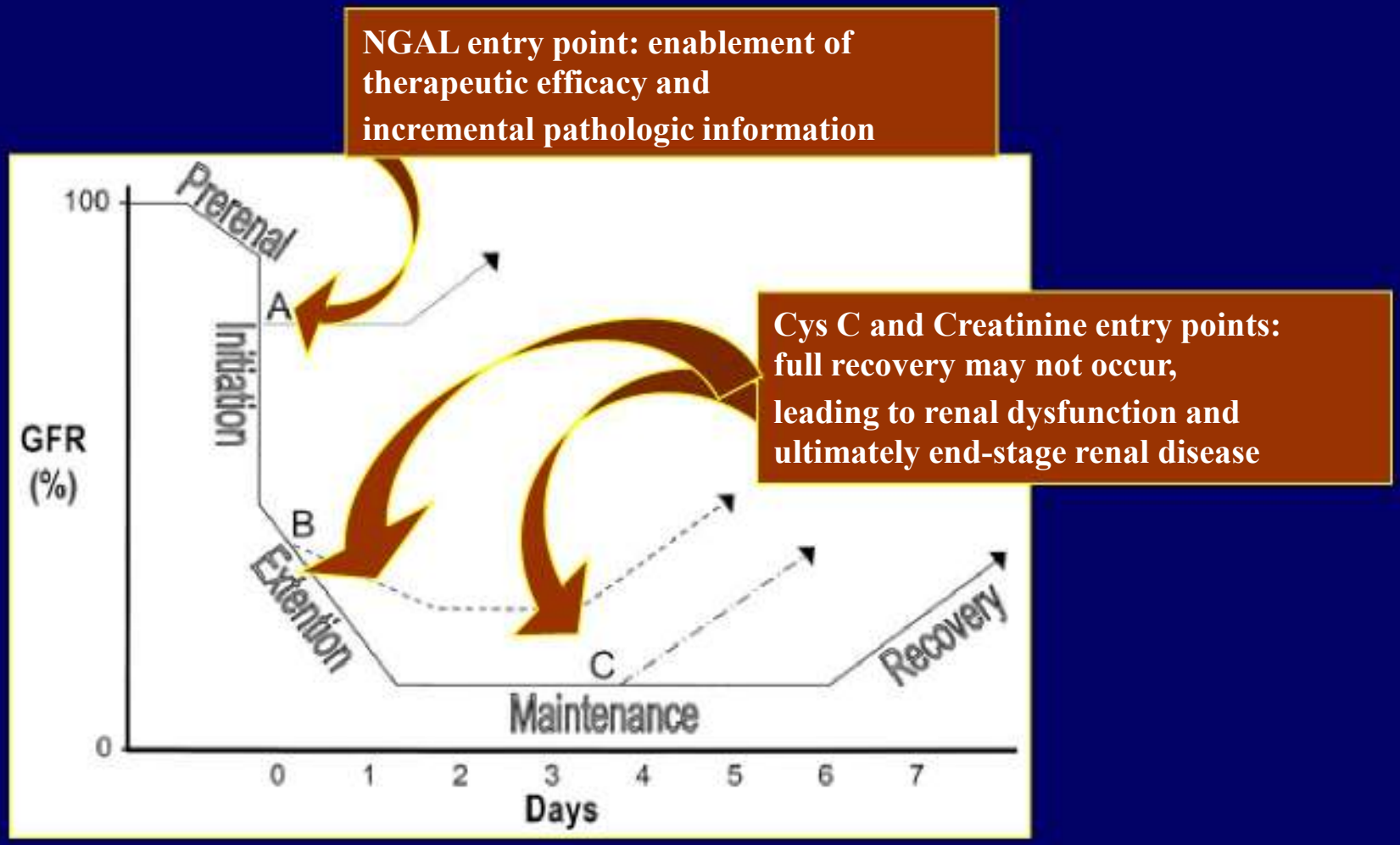
Vaidya VS, Ferguson MA, Bonventre JV. Biomarkers of Acute Kidney Injury.



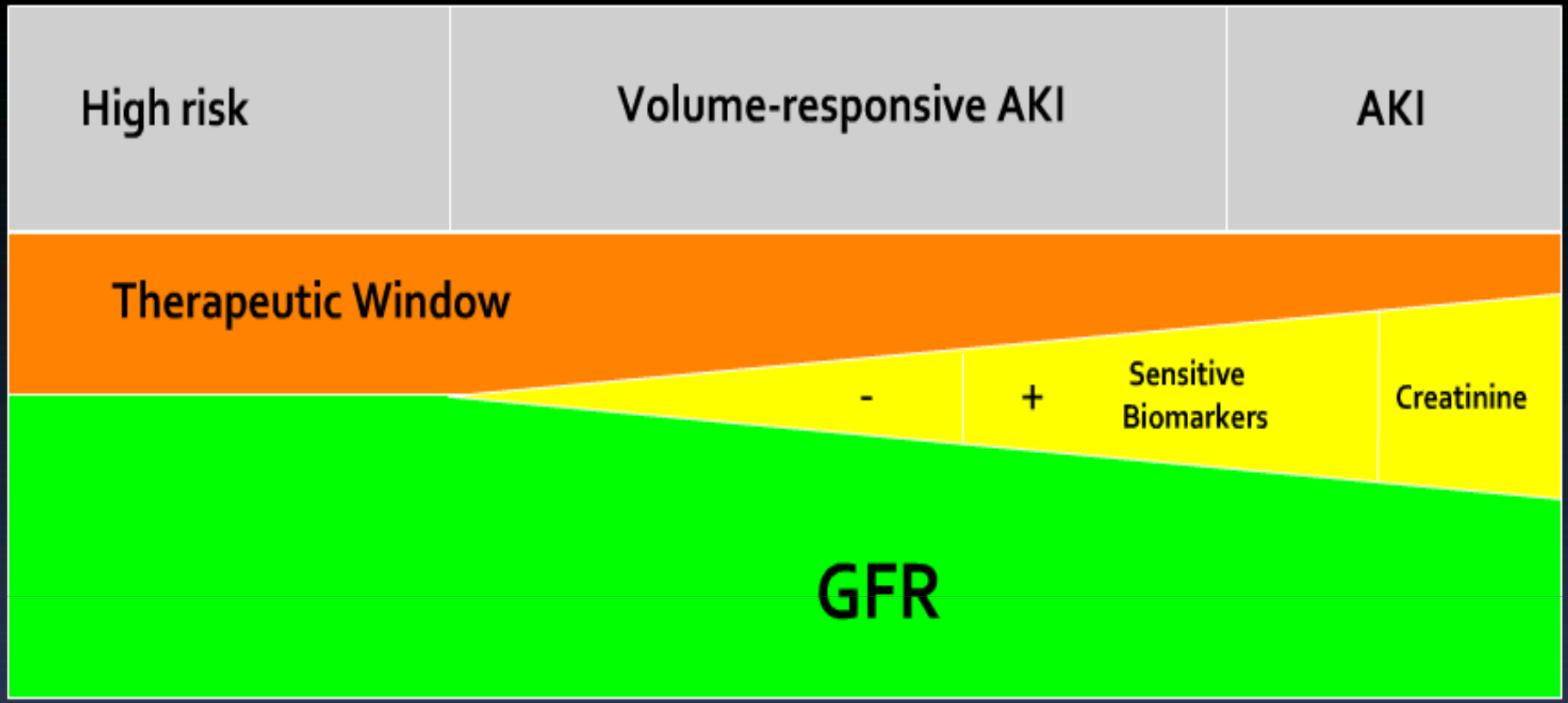


Molitoris BA, J Am Soc Nephrol 14:265-267, 2003

Earlier detection of AKI is needed



Adapted from Molitaris.JASN:2003; 14; 265

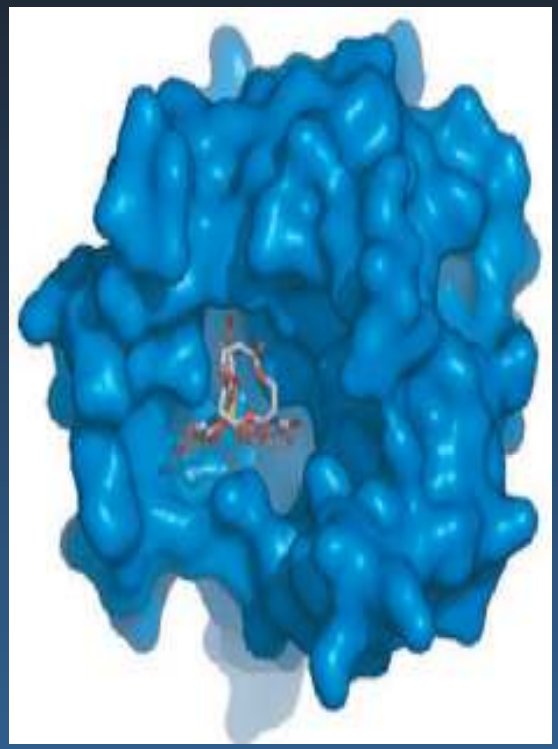


- Diagnosis relies on functional parameters (Cr, UOP)
- AKI is **more readily reversible in early stages**
- Need a more sensitive biomarker to detect early injury
  - Permit early targeted interventions to reverse or ameliorate AKI ("renal troponin")
  - Cystatin C, urinary NGAL, IL-18, etc.

What is NGAL?

Neutrophil gelatinase-asscociated lipocalin (NGAL)

- **First described as a 25 kDa protein bound to gelatinase from neutrophils**
- **Also known as lipocalin-2 and siderocalin.**
- **Known to play a role in fighting bacteria infections**

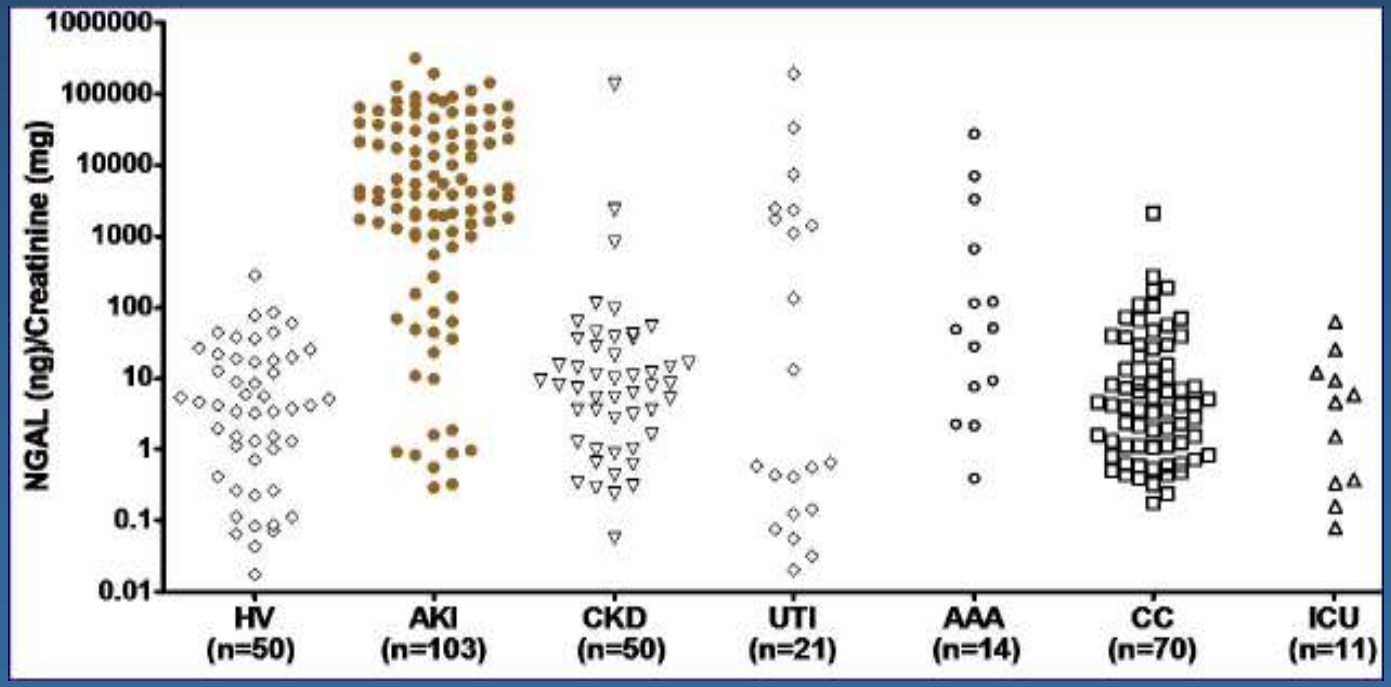


- **Animal studies have shown NGAL is one of the earliest proteins induced in the kidney after ischemic or nephrotoxic insult.**
- **Expanded studies have shown urinary NGAL to be an early marker of AKI in a variety of settings**

Honore, et al. Intensive Care Med 2007
Devarajan, Expert Opin Med Diag 2008
Waikar, et al. Clin J Am Soc Nephrol 2008

NGAL appears to detect AKI early

- Neutrophil Gelatinase-Associated Lipocalin
- Small (25kDa) protein first isolated from human neutrophils
- Secreted by immune cells, hepatocytes, and renal tubular cells in various physiologic states
- NGAL protein rapidly appears in plasma and urine following ischemic and nephrotoxic injury

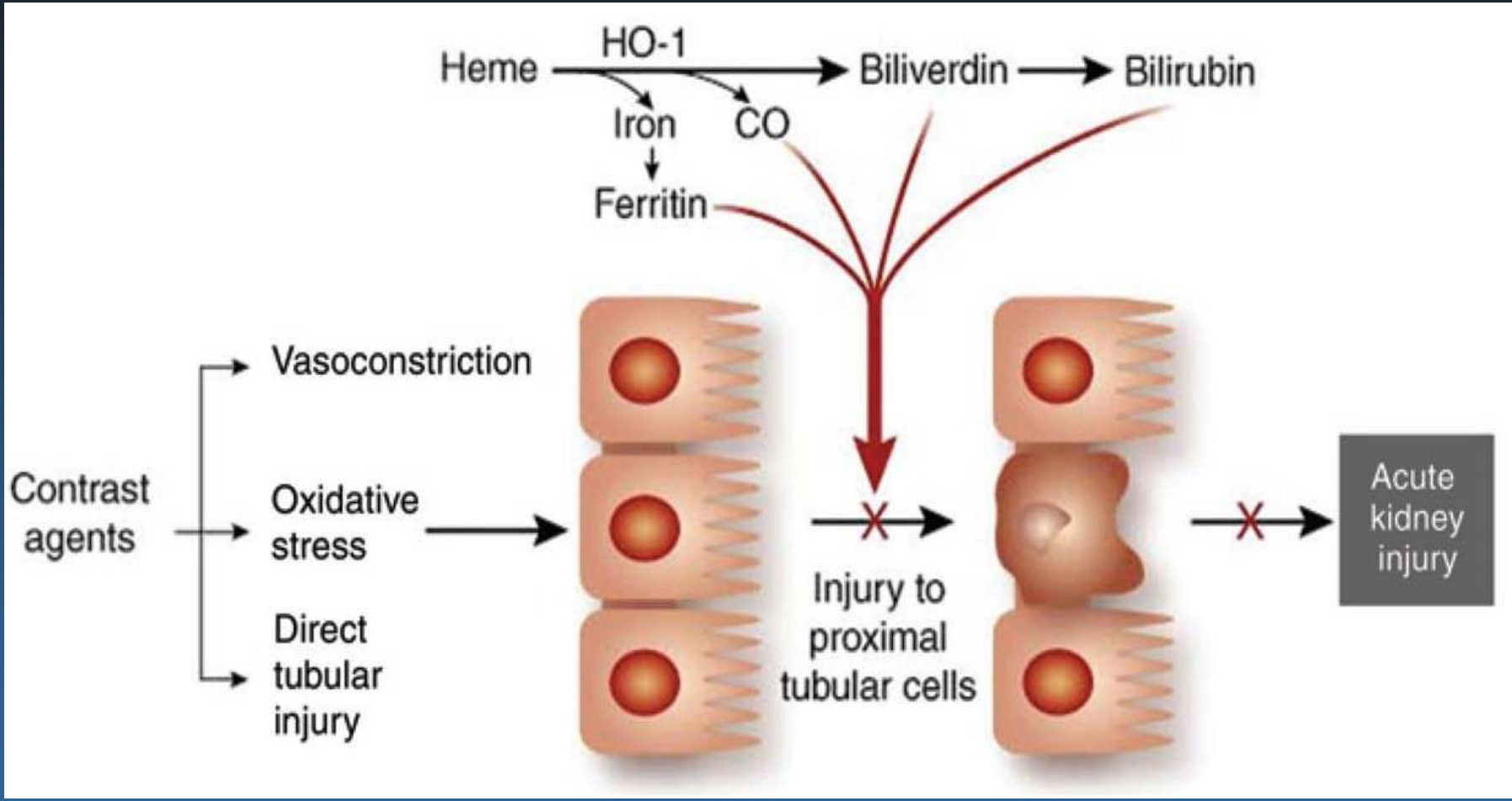


Mori J Clin Invest 2005

NGAL appears to detect AKI early

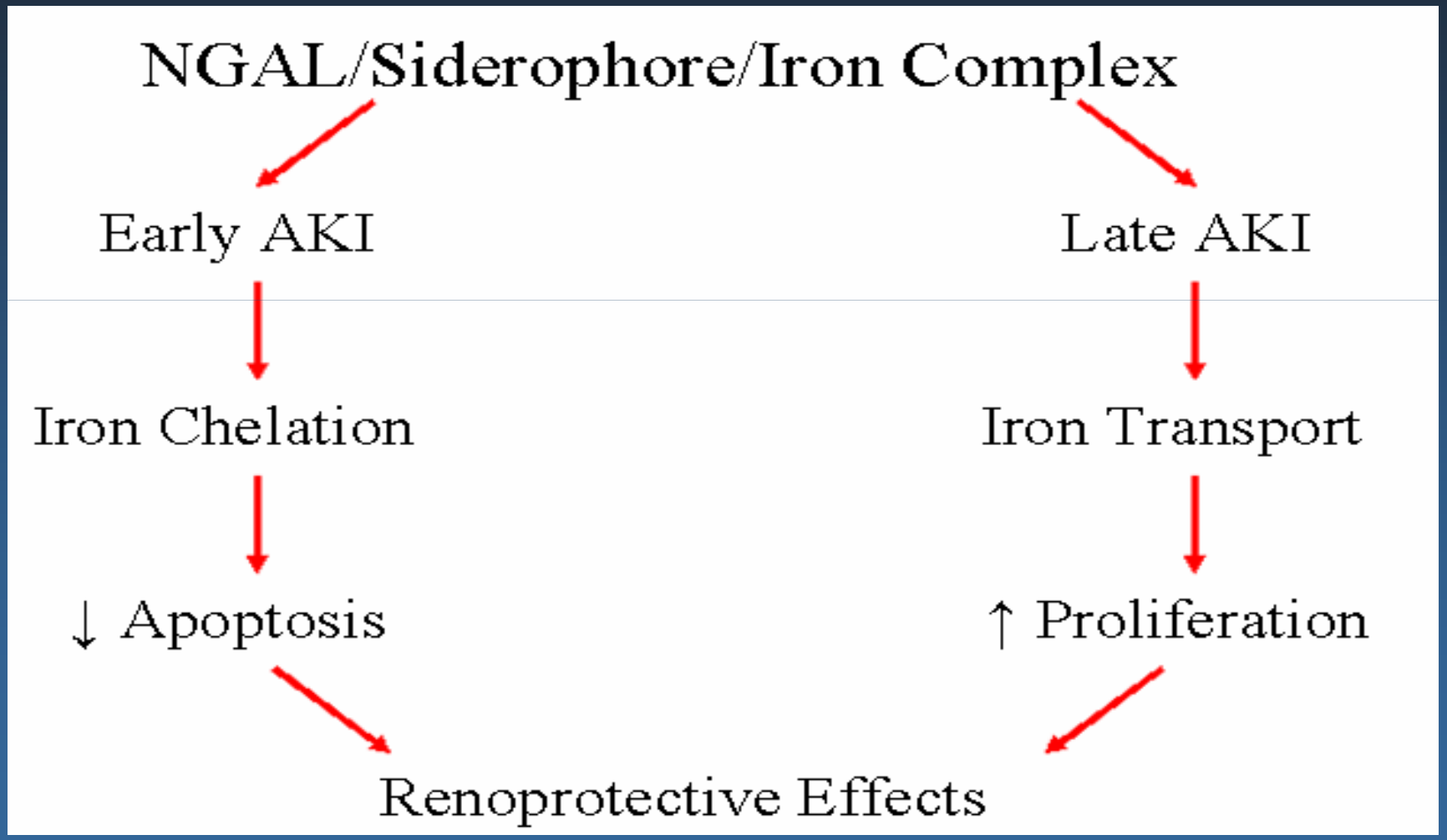
Application		Emerging NGAL Data
Detect AKI Following Cardiac Surgery	• The use of the cardiopulomonary bypass causes ischemic injury to the kidney • AKI following Cardiac Surgery has a high morbidity and mortality	√
Detect AKI in Patients Receiving Contrast	• Contrast dye used in imaging procedures is nephrotoxic and can cause AKI	√
Detect AKI in ED Patients	• All comers patients • Patients treated with diuretics for Acute HF often develop a worsening of renal function • Patients with suspected infection can develop AKI	√
AKI in Cardiorenal Syndrome	• 30% of patients treated for acute heart failure develop a worsening of their renal function	?

Protective action of NGAL

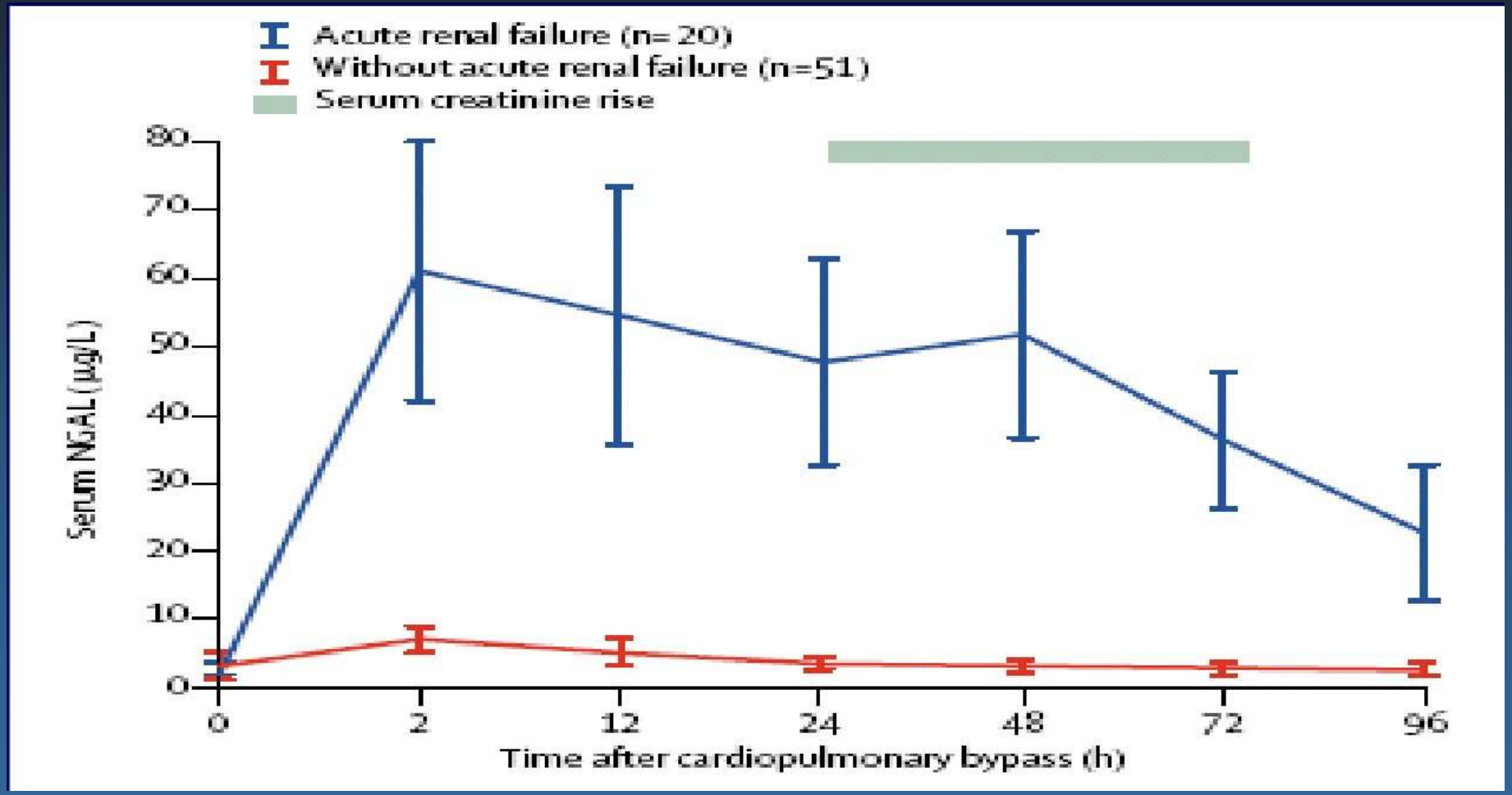


Exogenously administered NGAL “exerts remarkable protection in acute kidney injury through induction of HO-1.”

Role of NGAL in AKI pathophysiology



Translational phase: Serum NGAL analysis in CPB



Mishra et al, Lancet 365:1231-1238, 2005

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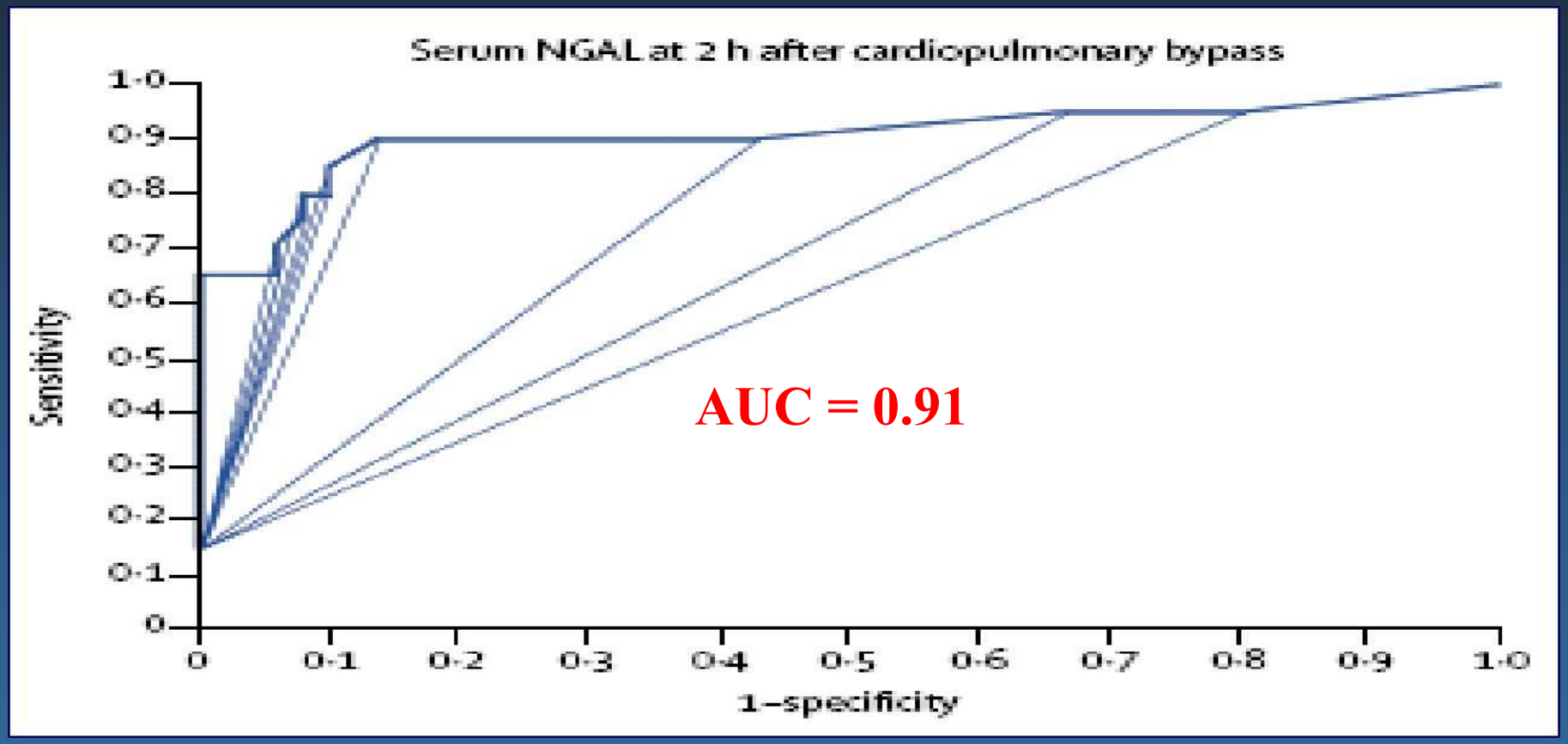
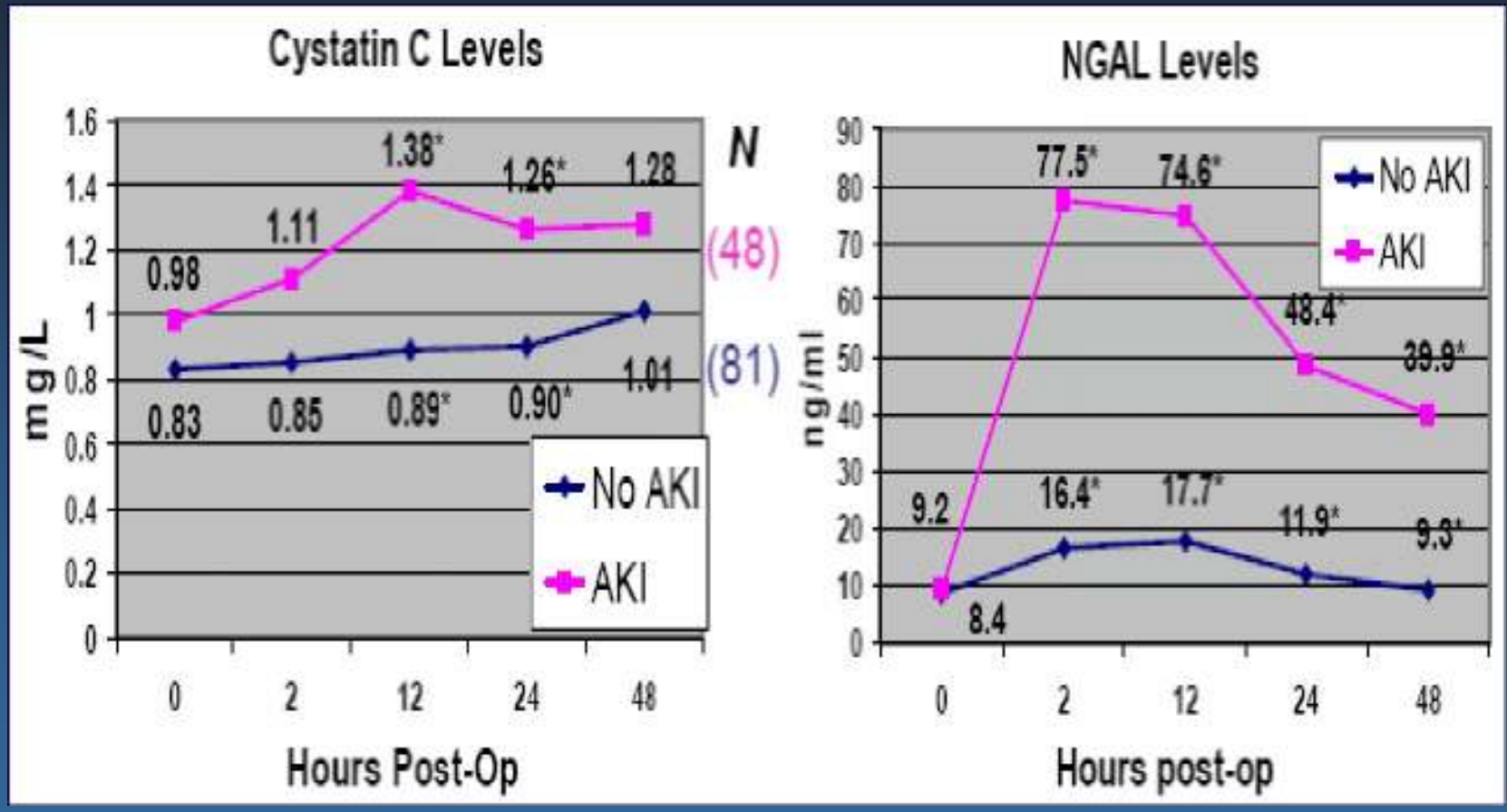


Mishra et al, Lancet 365:1231-1238, 2005

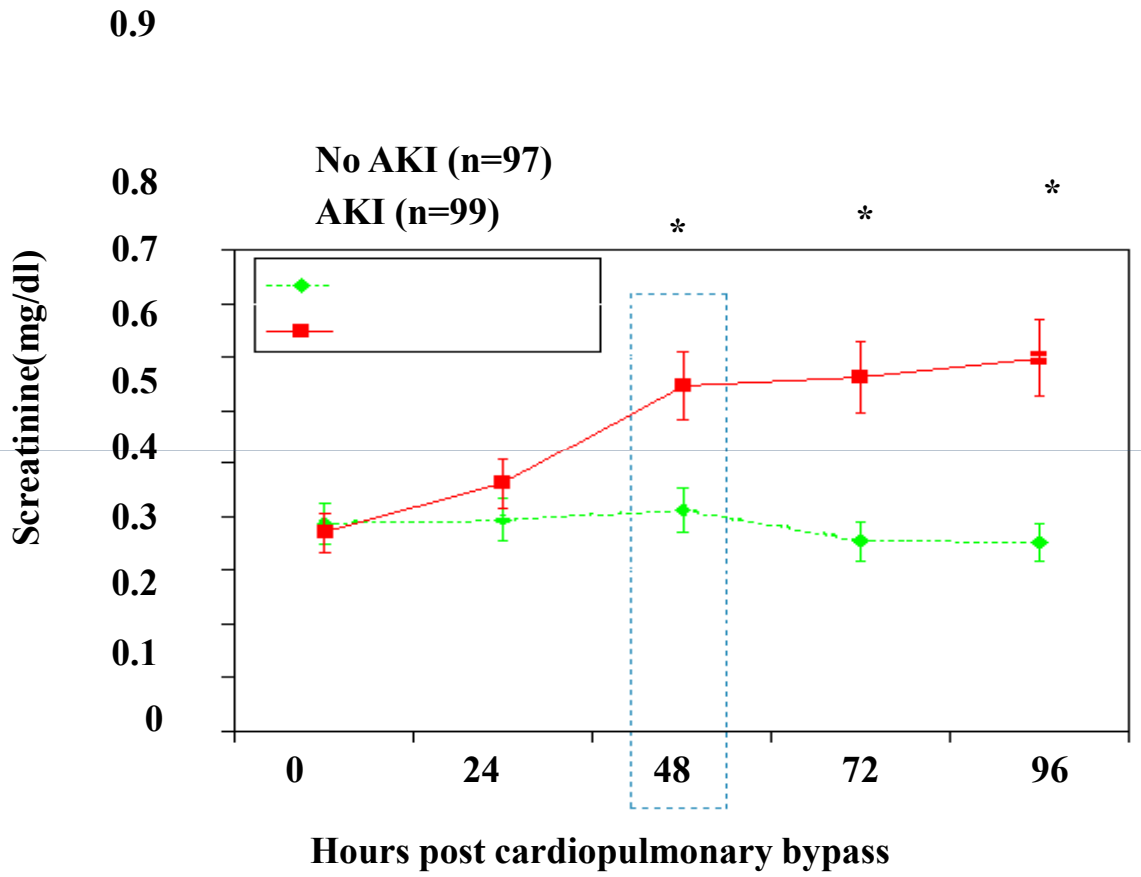
The emerging plasma AKI Panel: NGAL Vs Cystatin C



NGAL outperforms Cystatin C as a biomarker of AKI in CPB

Devarajan et al, JASN 17:404A, 2006

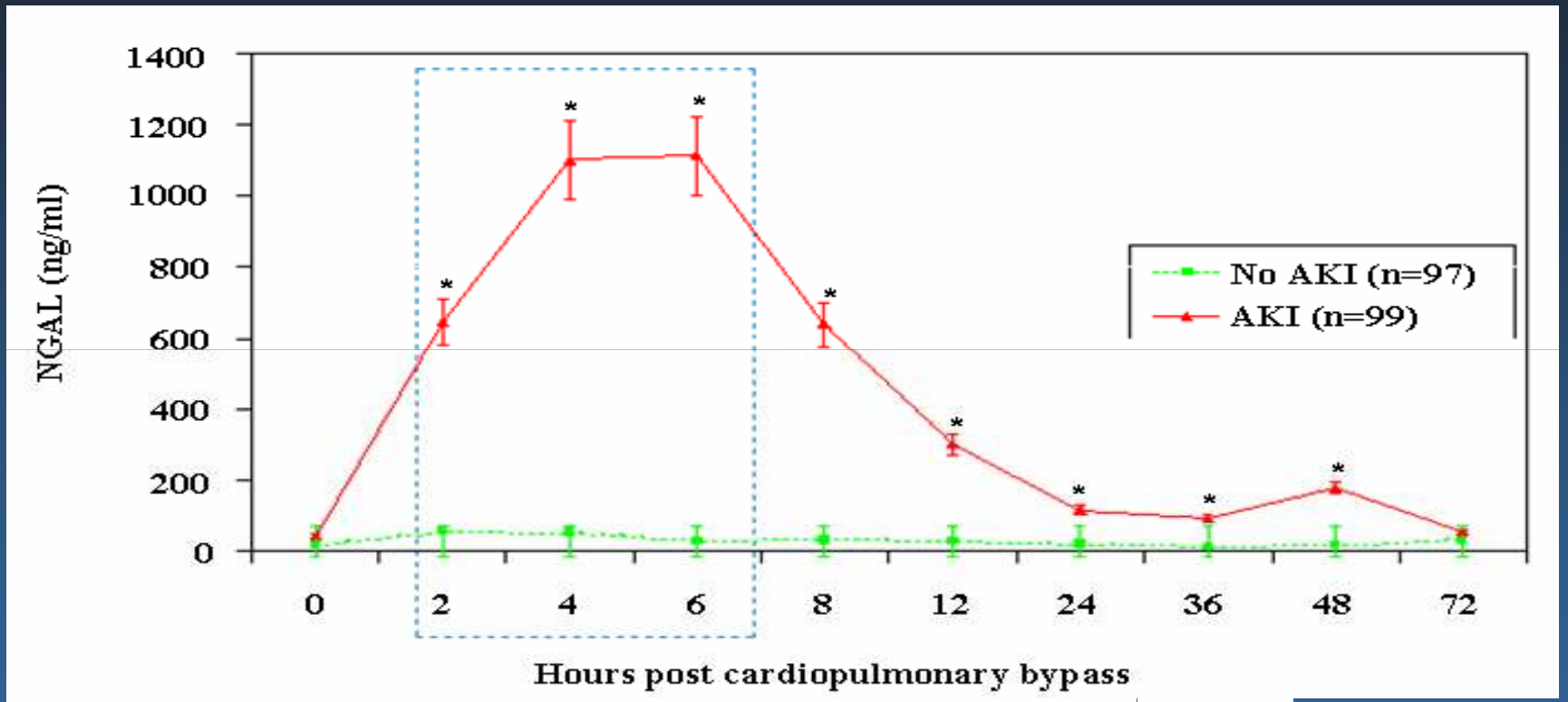
Serum creatinine post-CPB



*p < 0.05

Adapted from: Bennett et al., Clin J Am Soc Nephrol 2008

Urine NGAL measurements obtained by Architect assay* Post-CPB



AUC	0.93	0.96	0.98	0.94

*assay in development

*p < 0.05

Adapted from: Bennett et al., Clin J Am Soc Nephrol 2008

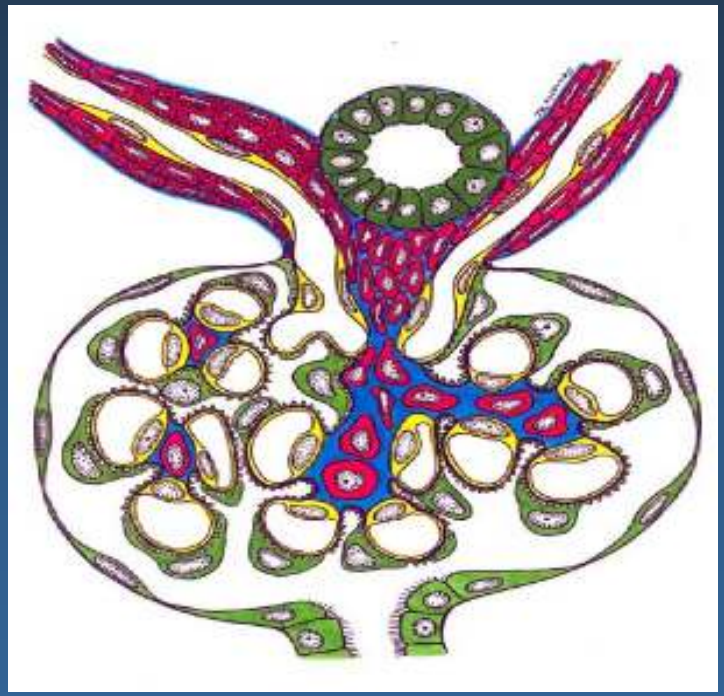
Diagnosis and monitoring of AKI

Coca SG et al, Kidney Int Dec 19, 2007

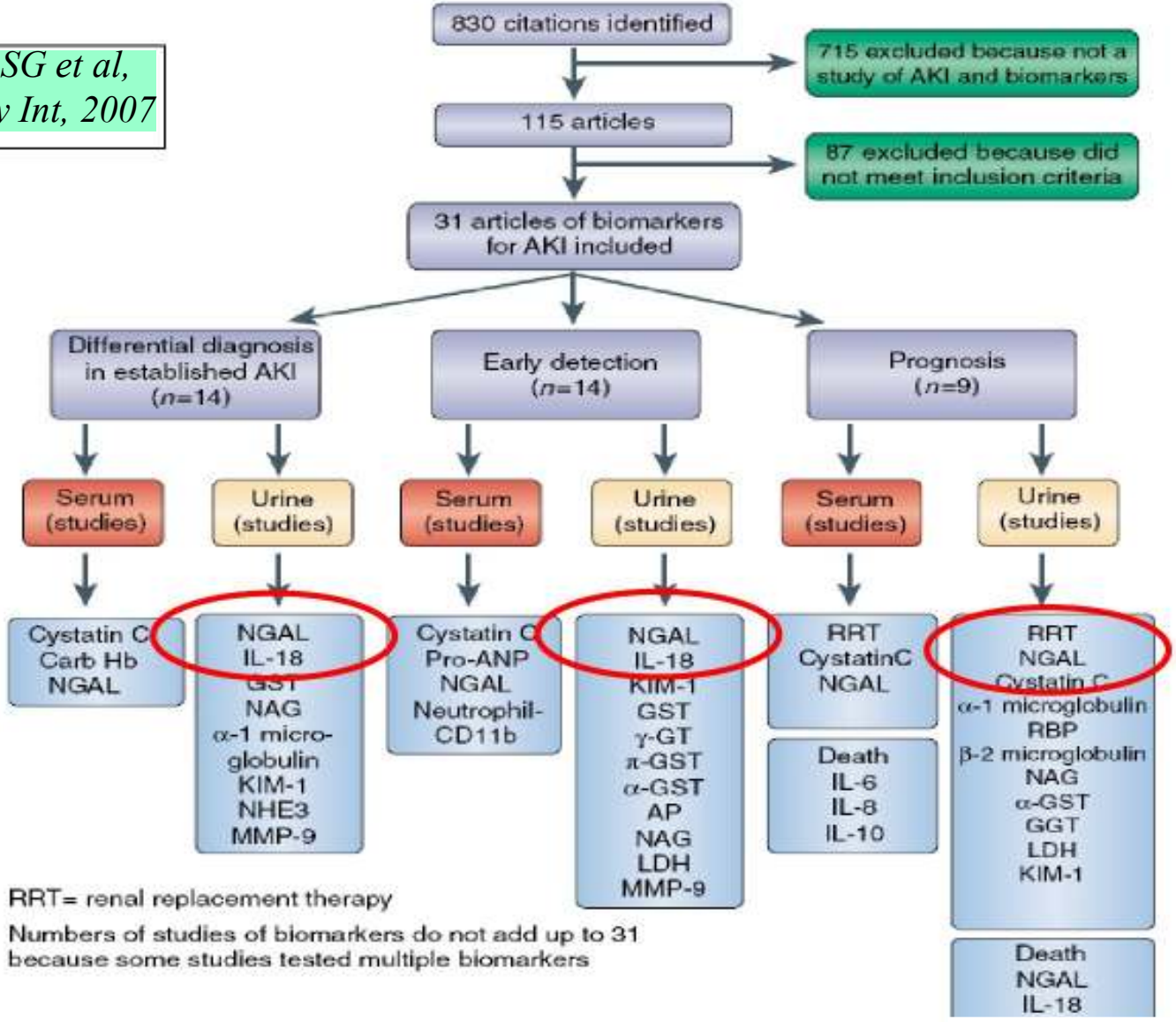
Established AKI

Early AKI

Severity of AKI



Coca SG et al, Kidney Int, 2007



25 studies had "good" methodological quality

Potential benefits of urine NGAL testing

- Early diagnosis and initiation of therapeutic measures
  - Risk stratification
  - Predict clinical outcomes (e.g., length of hospital stay mortality)
  - Monitor response to therapy
  - Facilitate clinical trials

Potential application for NGAL?

- If renal injury in HF patients could be identified early, alterations in treatment could occur
- Can NGAL identify early kidney injury in HF before functional loss
- Studies currently underway

GALLANT-CHF

- n GAL evaluation
  Along with Natiuretic
  peptides in CHF

Conclusion

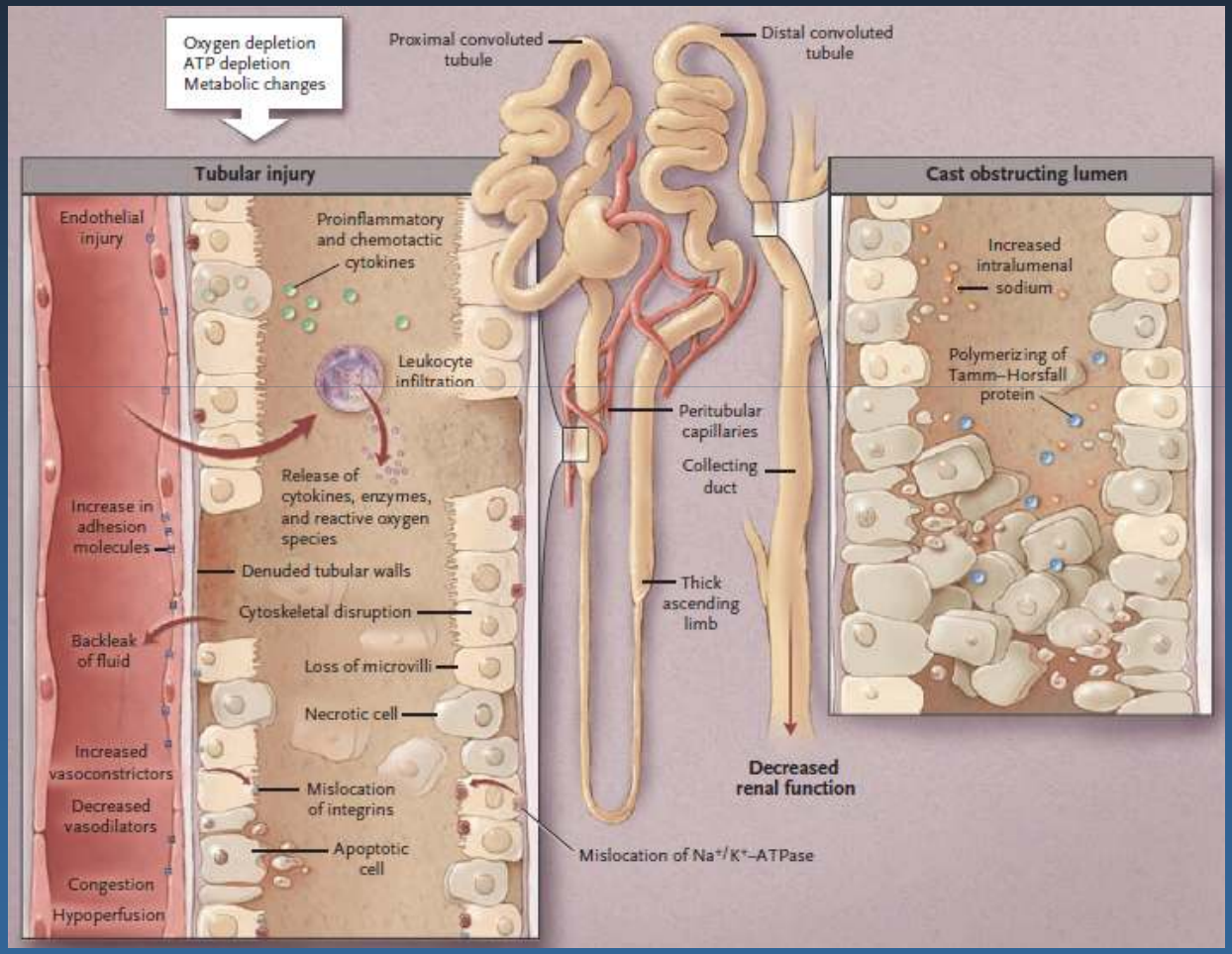
The alarm of the clinical clock is always late for an early intervention.

NGAL provides promise as an early biomarker of acute kidney injury.


By Denise M
Obrigada
(Thank You)

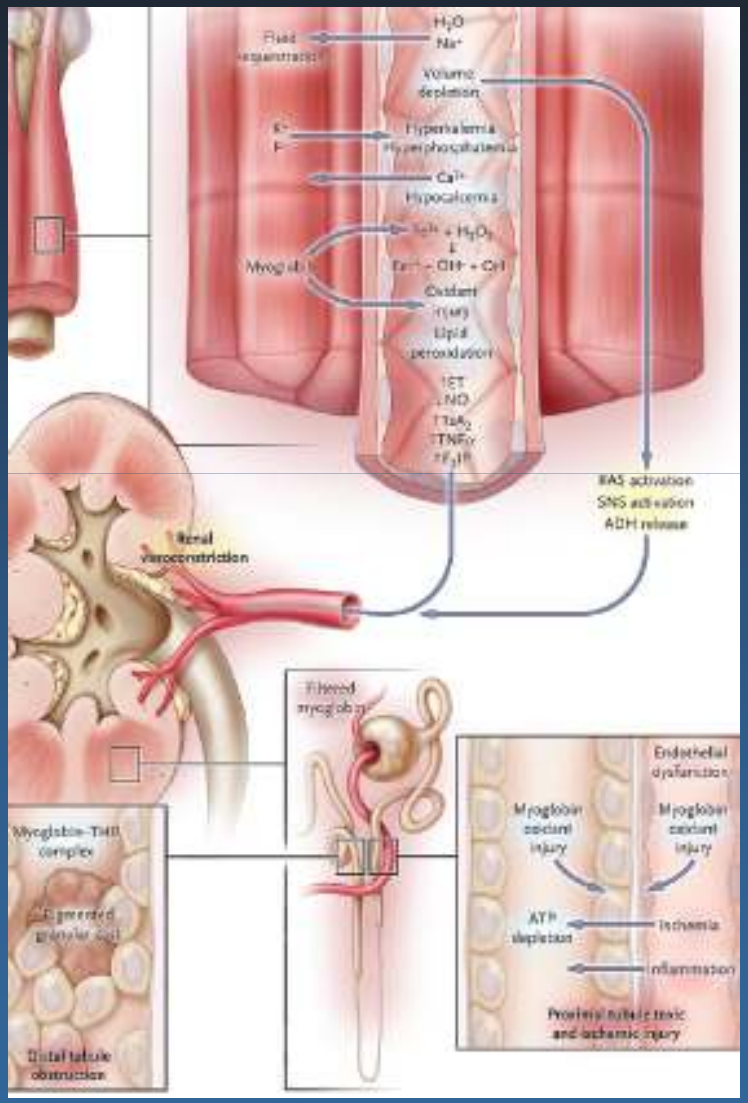
Case-1

Ischemic acute tubular necrosis



Abuelo JG. NEJM. 2007;357(8):797-805.

Rhabdomyolysis



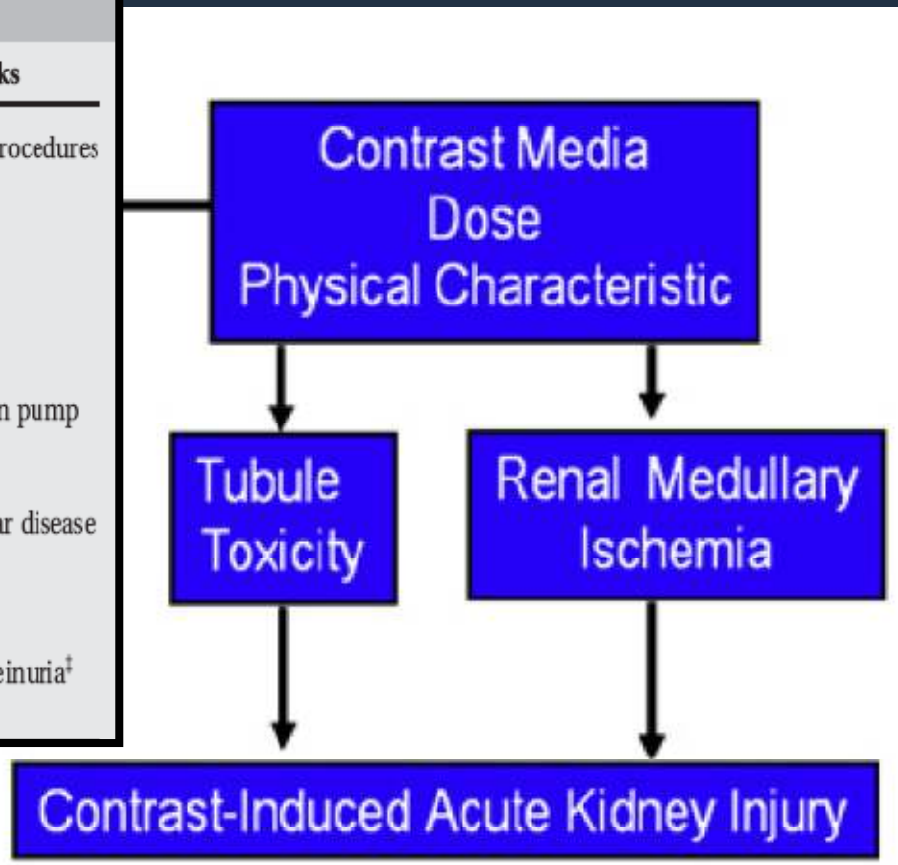
Bosch X. NEJM. 2009;361(1):62-72.

Case -2

Contrast Induced AKI

TABLE 1. Risk Factors for Contrast Nephropathy

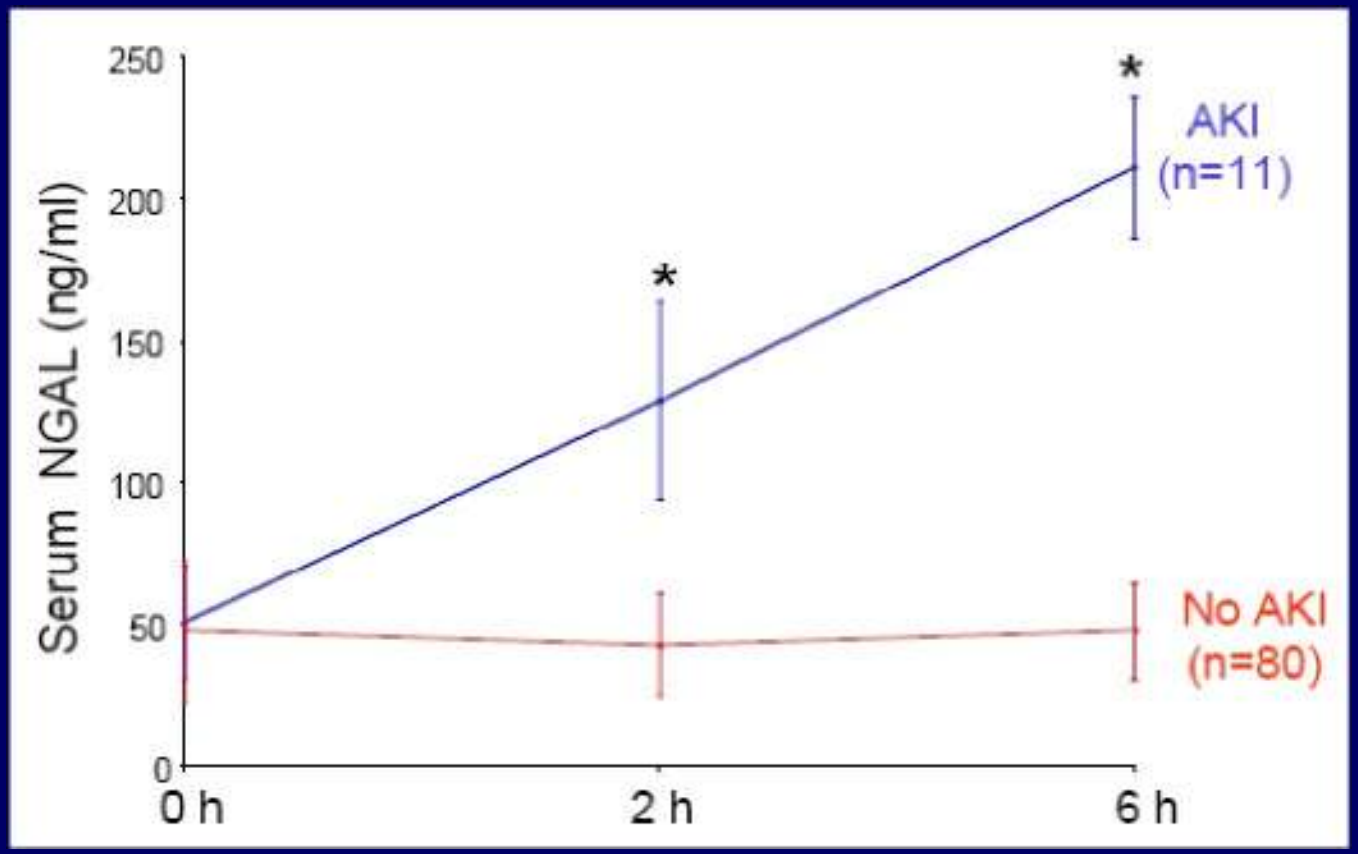
Clear Risks	Probable Risks	Questionable Risks
Estimated GFR <60 mL/minute/1.73 m^2, especially if due to diabetic nephropathy*	Diabetes mellitus*	Repeat contrast procedures
	Concomitant use of nephrotoxic drugs	Age >75 years
	Hemodynamic instability	Male gender
	Congestive heart failure	Intraaortic balloon pump
	Large contrast volume (>100 mL)†	Liver disease
	Intraarterial contrast administration	Peripheral vascular disease
		Hypertension
		Anemia
		Bence-Jones proteinuria†
		Hyperuricemia



Abu Jawdeh BJ. J Hosp Med. 2009;4:500–506.

Solomon R. Radiol Clin N Am. 2009;47:783–788

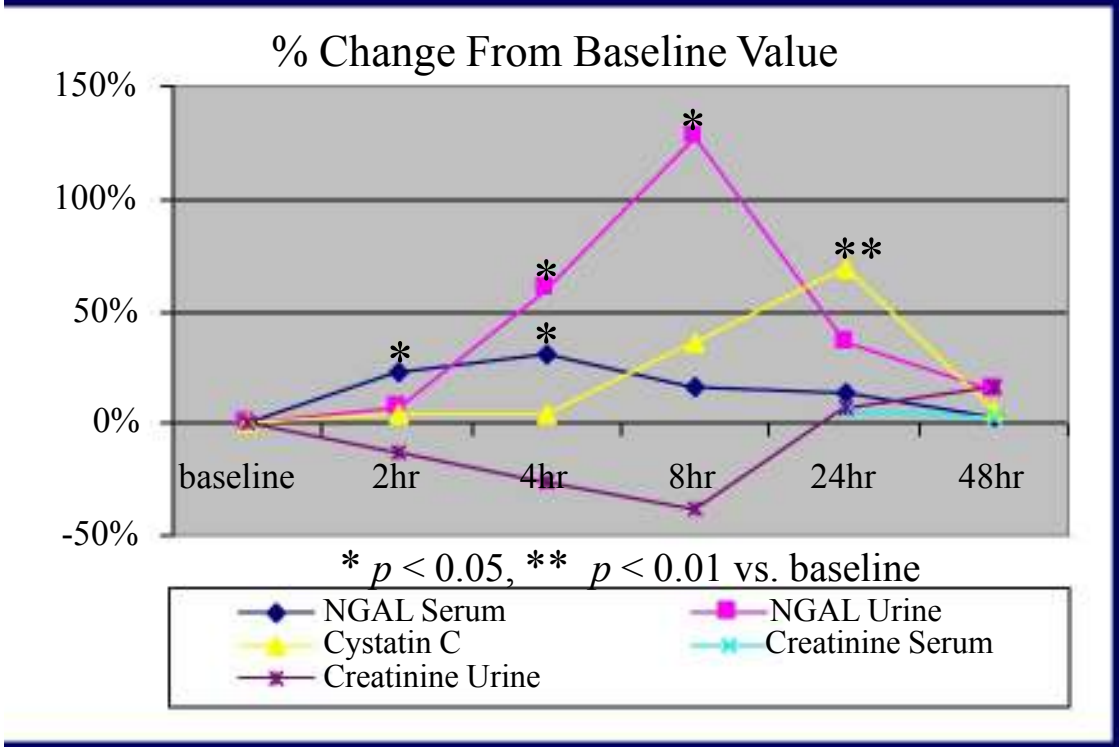
Contrast Induced AKI in Children



- Serum NGAL is significantly elevated by 2 hrs post-contrast administration

Devarajan JASN 17:404A, 2006

Contrast Induced AKI in Adults



- Serum NGAL is significantly elevated by 2 hrs post-contrast administration

	Plasma NGAL	Urine NGAL
Sensitivity	**90%**	**76%**
Specificity	**74%**	**80%**

Bachorzewska-Gajewska et al., NTD 2006
Bachorzewska-Gajewska et al. Int J Cardiol (2007)