

Subject....

February 2010

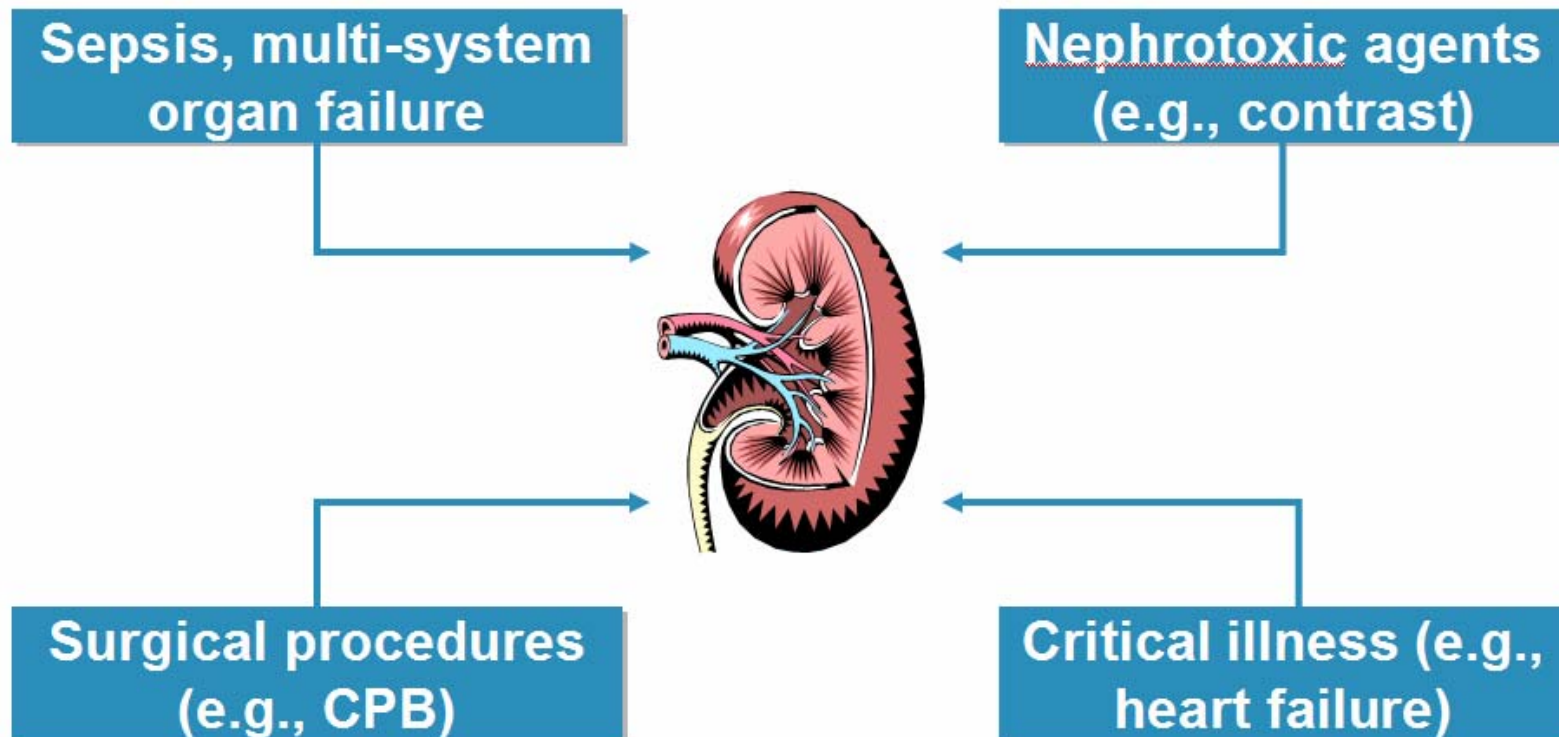
Urine NGAL - a novel biomarker for acute kidney injury (AKI)

A Troponin for the Kidney?

What is Acute Kidney Injury (AKI)?

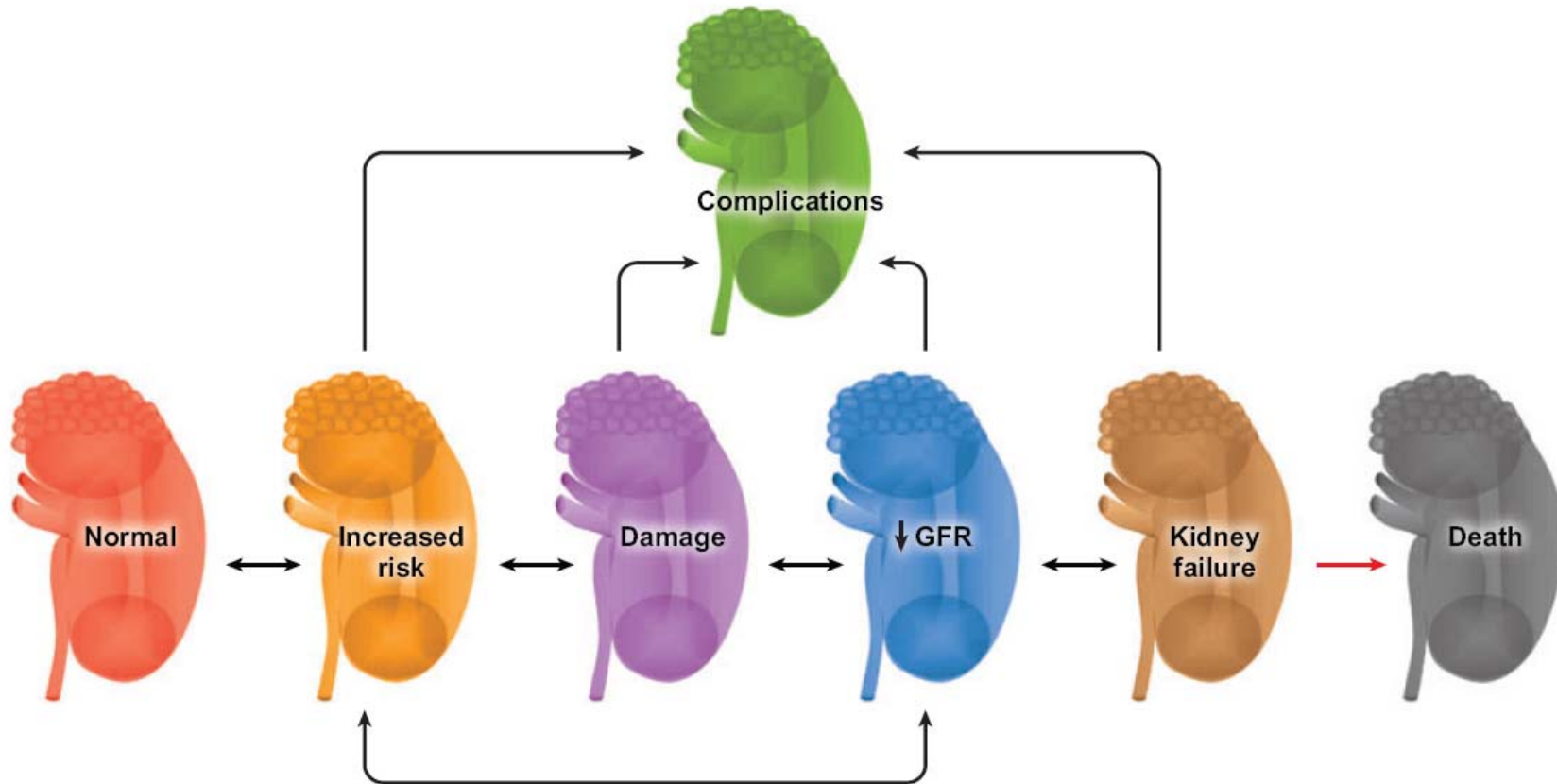
- Acute kidney injury (AKI) is a common and devastating problem in clinical medicine. Previously known as acute renal failure (ARF).
- Characterized by an abrupt (hours to days) decline in kidney function. Diagnosis usually based on either an elevation of serum creatinine and/or detection of decreased urine production (oliguria).
- Occurs in a variety of clinical settings. Incidence varies from ~ 5% of hospitalized patients to > 30% of ICU patients, and is increasing dramatically.
- Associated with significantly increased cost of care and substantial morbidity and mortality (e.g., 4 million attributable deaths worldwide per year)

Common causes of AKI (hospital-acquired)



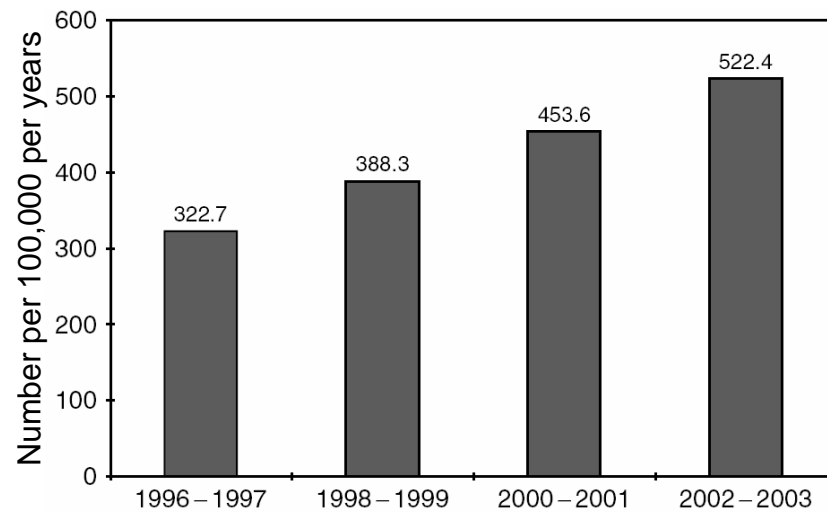
Adapted from Parikh and Devarajan, Crit Care Med 2008

Kidney injury continuum



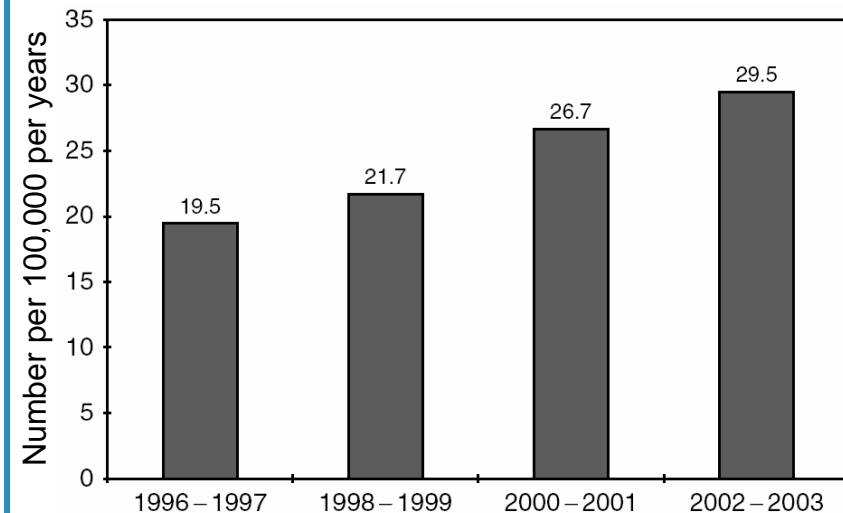
Community-based AKI incidence rates

AKI Not Requiring Dialysis



> 60% increase from 1996 to 2003

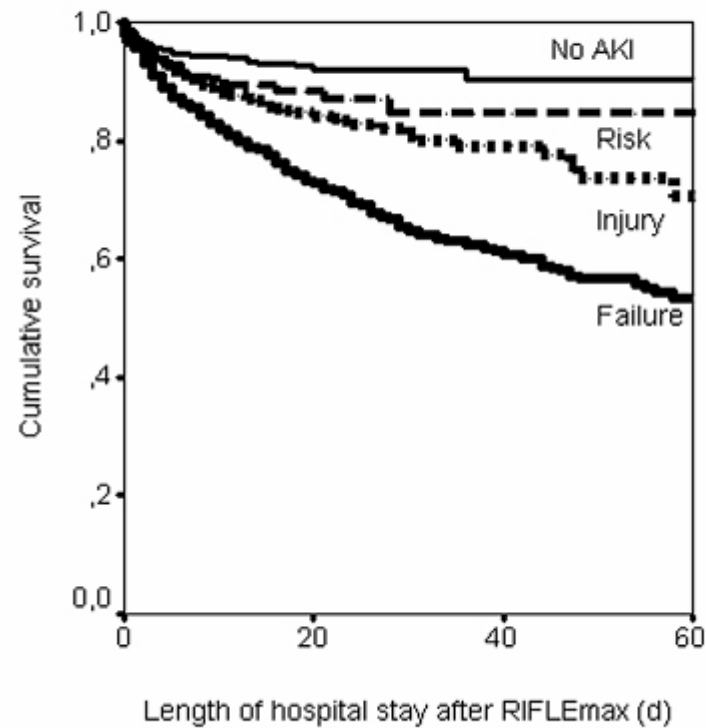
AKI Requiring Dialysis



> 50% increase from 1996 to 2003

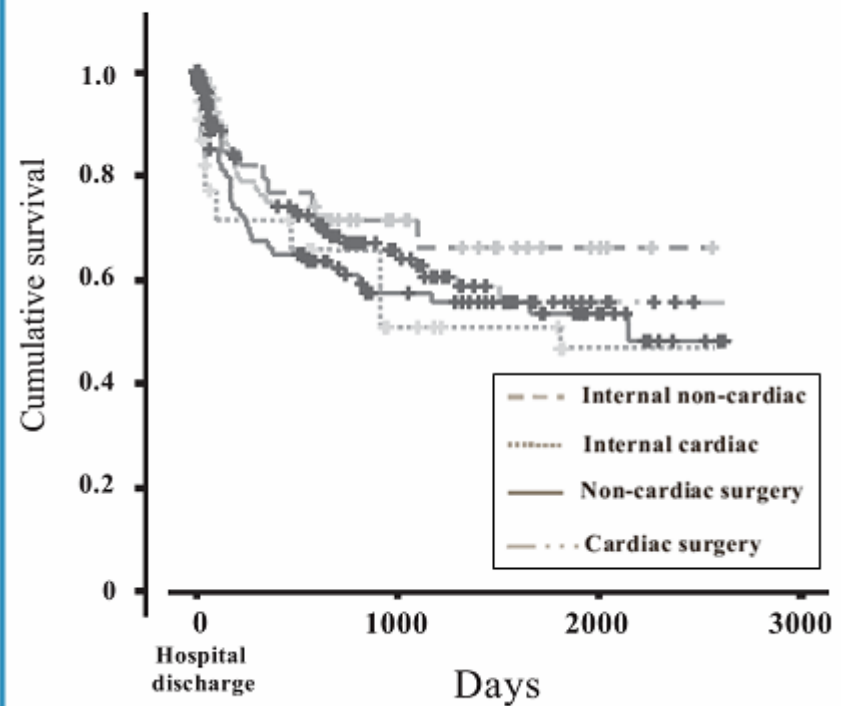
Survival of AKI patients

In Hospital



Hoste, et al. Crit Care 2006

Out of Hospital



Morgera, et al. Crit Care Med 2008

Limitations of current methods for diagnosing AKI

AKI is typically diagnosed as a rise in serum creatinine.

However, creatinine is not a good marker during acute changes in kidney function

- Serum creatinine is not specific for kidney injury, and levels can vary widely depending on a large number of non-renal factors (e.g., age, gender, muscle mass, hydration status, etc.)
- Because of large renal reserve, up to 50% of kidney function may be lost before serum creatinine rises
- Serum creatinine does not accurately depict kidney function until steady state has been achieved (up to 2 – 3 days after injury)

It is likely that the use of serum creatinine as a therapeutic trigger in clinical trials has resulted in the failure of promising therapeutic interventions

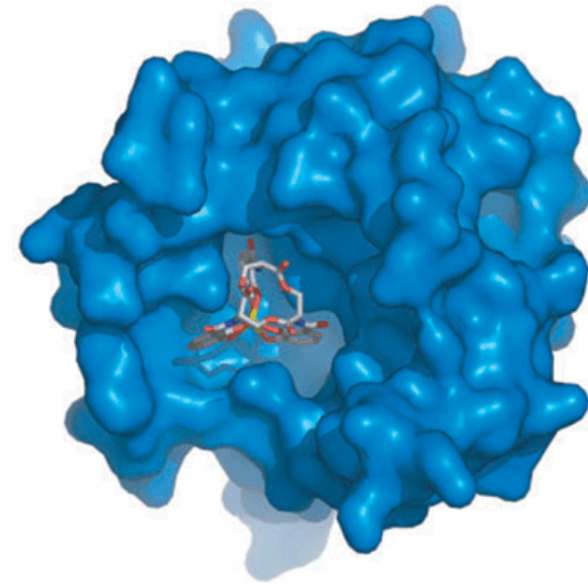
The failure of creatinine as a marker for AKI

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

“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.”

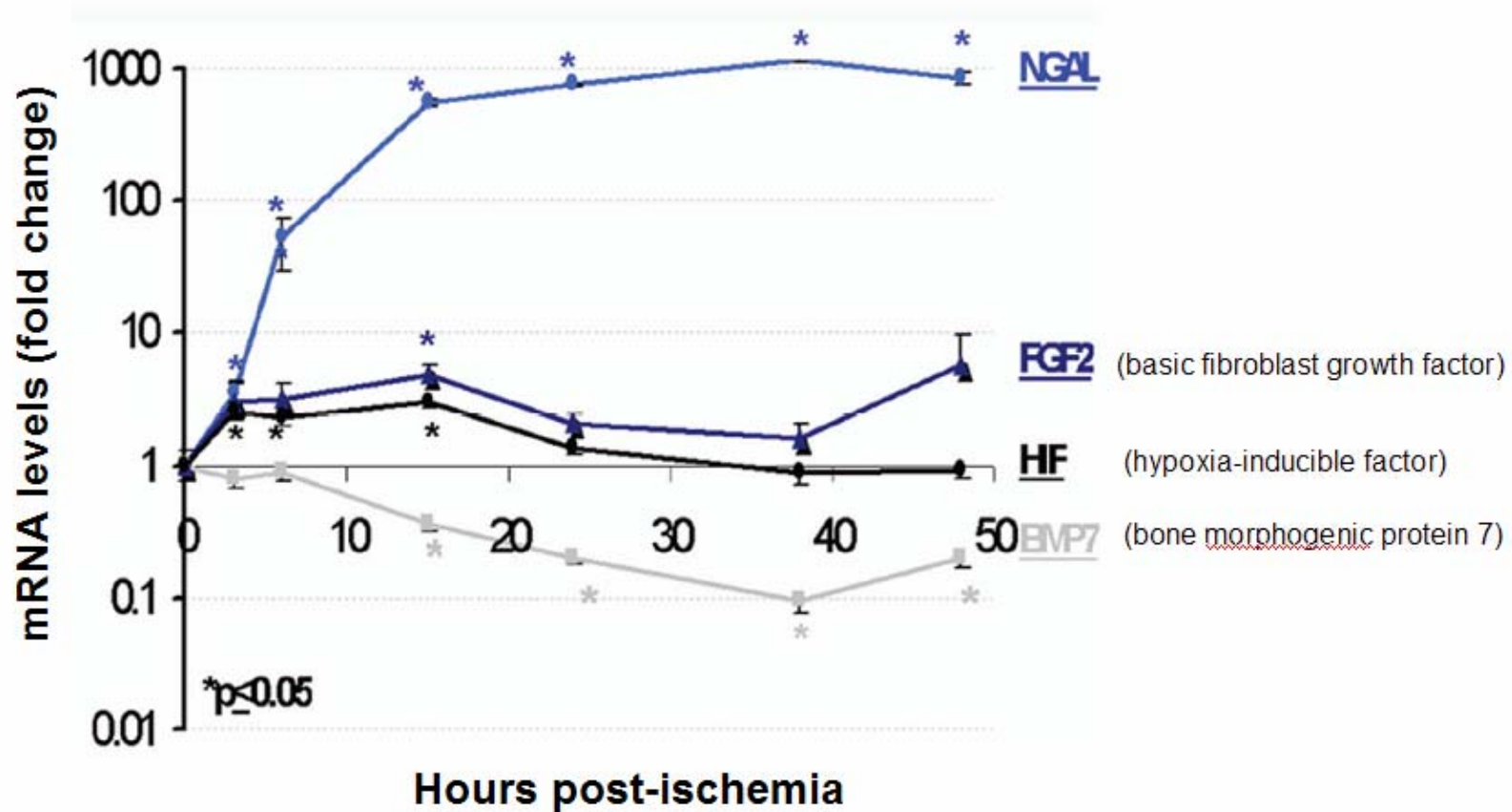
What is NGAL?

- Neutrophil gelatinase-associated 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.



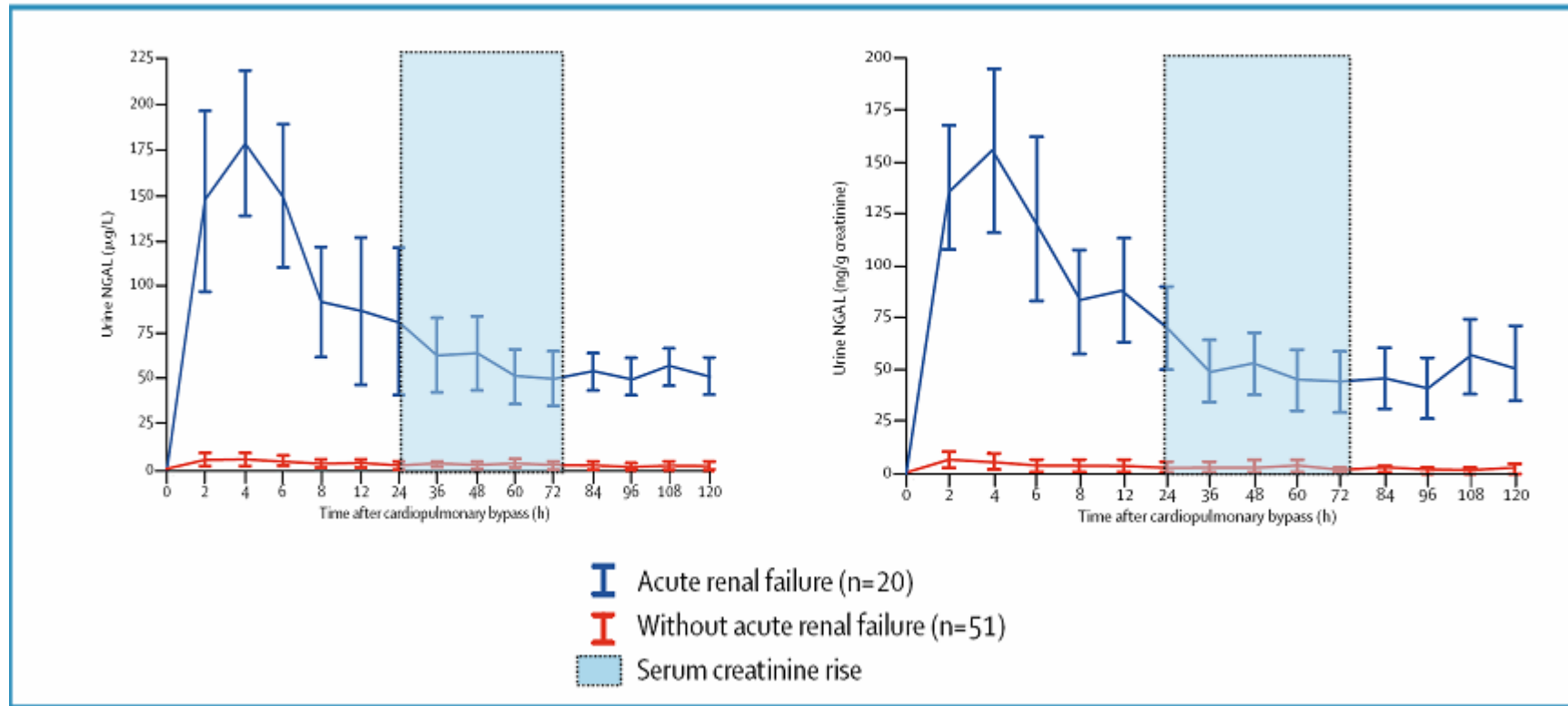
Crystal structure of NGAL bound to Fe(III)-Enterobactin (Fishbach, et al. Nat Chem Biol 2006)

Ischemic kidneys synthesize NGAL



Adapted from: Schmidt-Ott, et al. JASN 2007

Urine NGAL levels after cardiac surgery



Adapted from Mishra, *et al.* Lancet 2005

Urine and serum NGAL test characteristics

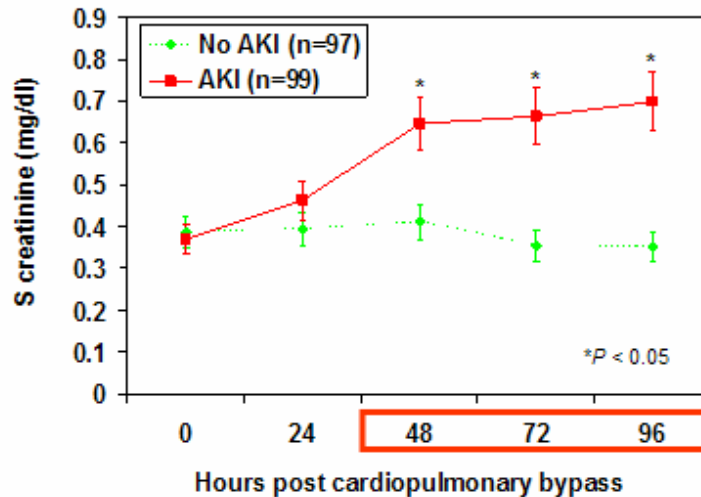
	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Cutoffs for 2-h urine NGAL				
25 µg/L	1.00	0.98	0.95	1.00
50 µg/L	1.00	0.98	0.95	1.00
80 µg/L	0.90	1.00	1.00	0.96
100 µg/L	0.70	1.00	1.00	0.89
Cutoffs for 4-h urine NGAL				
25 µg/L	1.00	0.96	0.91	1.00
50 µg/L	0.95	1.00	0.95	0.98
80 µg/L	0.70	1.00	1.00	0.89
100 µg/L	0.65	1.00	1.00	0.88
Cutoffs for 2-h serum NGAL				
25 µg/L	0.70	0.94	0.82	0.89
50 µg/L	0.50	1.00	1.00	0.84
80 µg/L	0.20	1.00	1.00	0.76

AUC at 2 hours post surgery: Urine = 0.998 Serum = 0.906

Urine NGAL levels after cardiac surgery

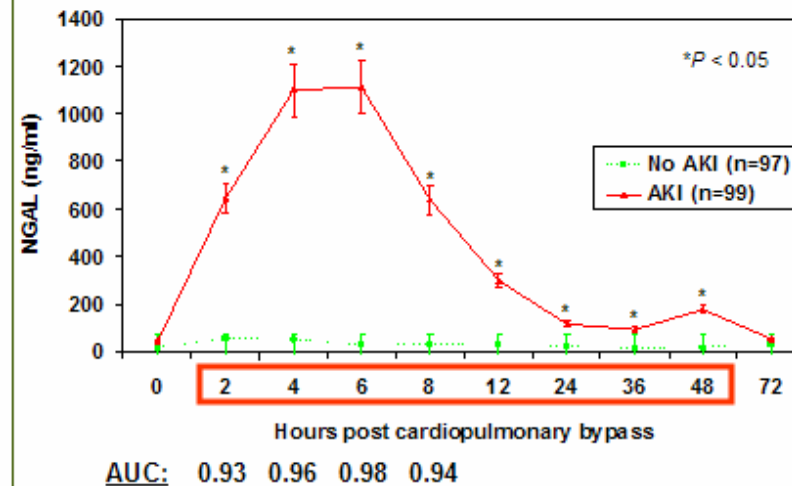
Serum creatinine measurements* obtained at various time points post-CPB.

AKI, acute kidney injury, defined as a 50% increase in serum creatinine from baseline.



Urine NGAL measurements* obtained by ARCHITECT assay at various time points post-CPB.

AKI, acute kidney injury, defined as a 50% increase in serum creatinine from baseline.

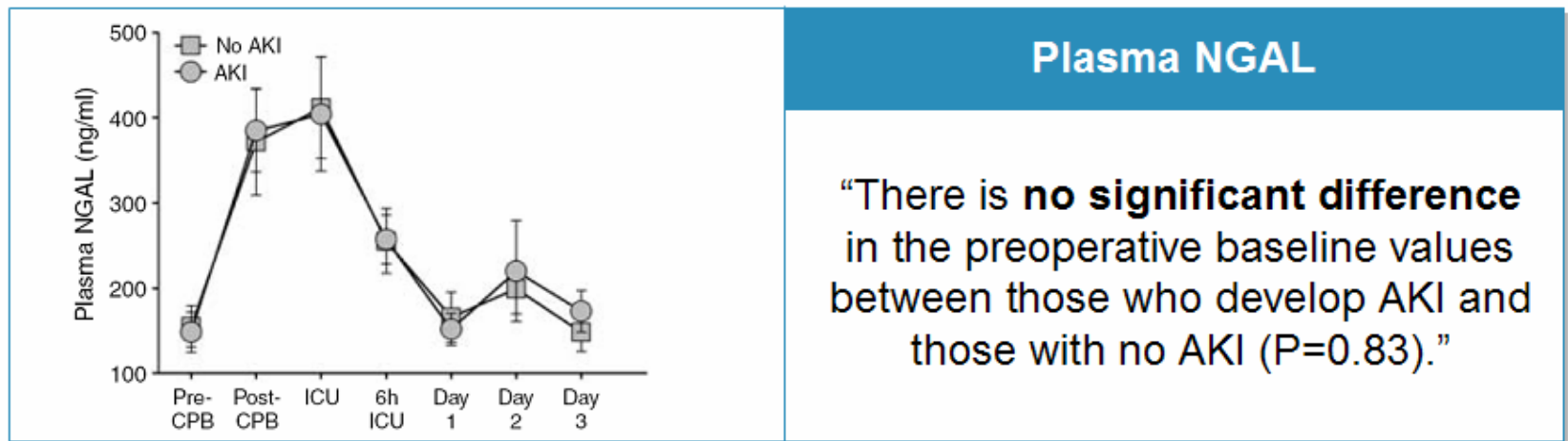
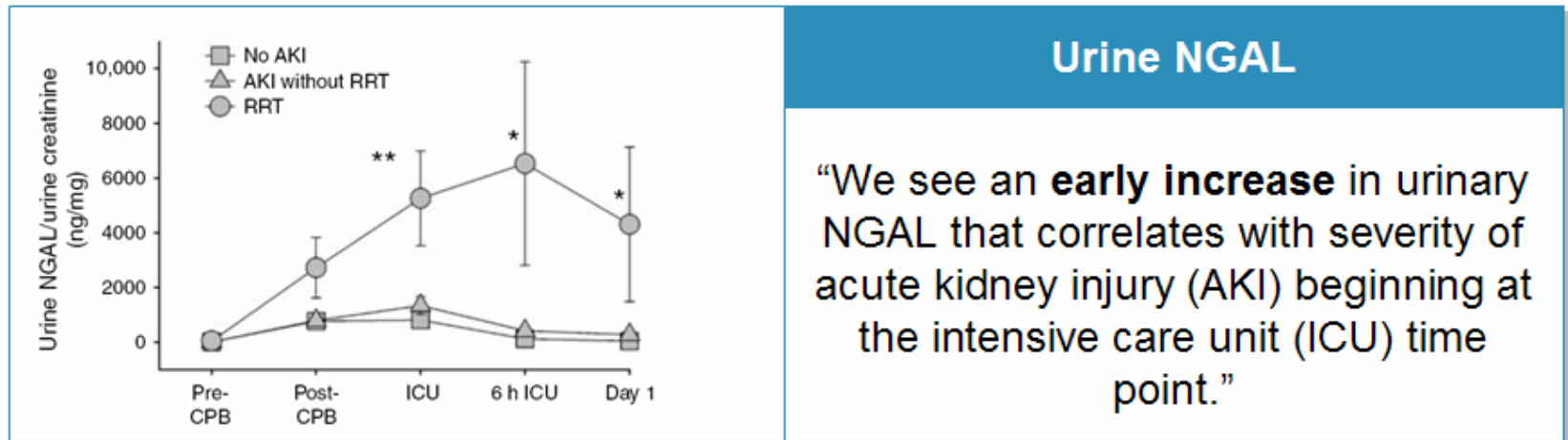


Urine NGAL represents an early predictive biomarker of AKI severity after CPB.*

Conclusions of Bennett et al.

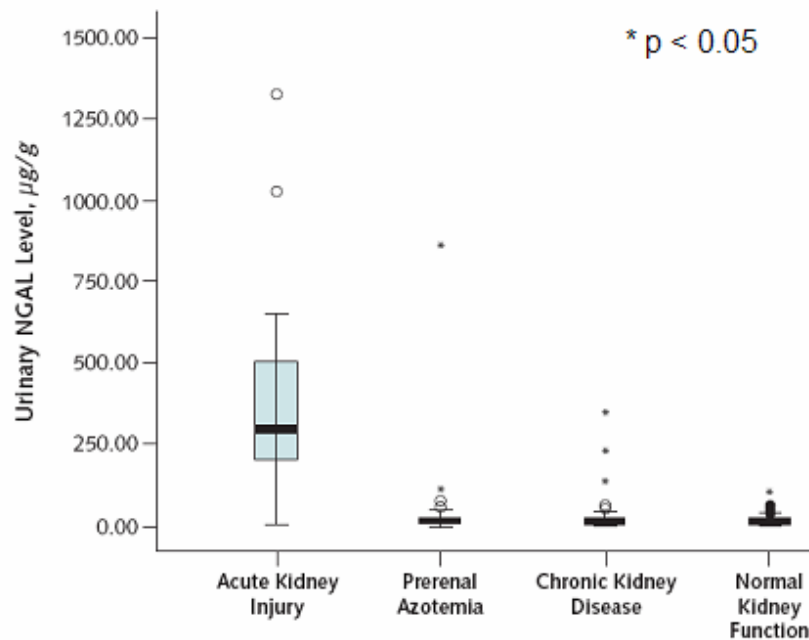
- “... urine NGAL levels measured by the ARCHITECT assay at several early time points after CPB were excellent biomarkers for the subsequent development of AKI and its complications.”
- “The magnitude of rise supports the notion that urine NGAL ... (would) allow for easy risk stratification.”
- Urine NGAL was associated with key clinical factors, including length of stay ($p < 0.0001$), days in AKI ($p < 0.001$) need for dialysis ($p = 0.01$, AUC = 0.86), and death ($p = 0.01$, AUC = 0.91).
- “... availability of promising early biomarkers may enable the timely initiation of interventions ... (and) the availability of a standardized commercial platform for urinary NGAL ... will enable these safe and highly promising agents to be investigated in humans with AKI.”

Urine and Plasma NGAL levels after cardiac surgery



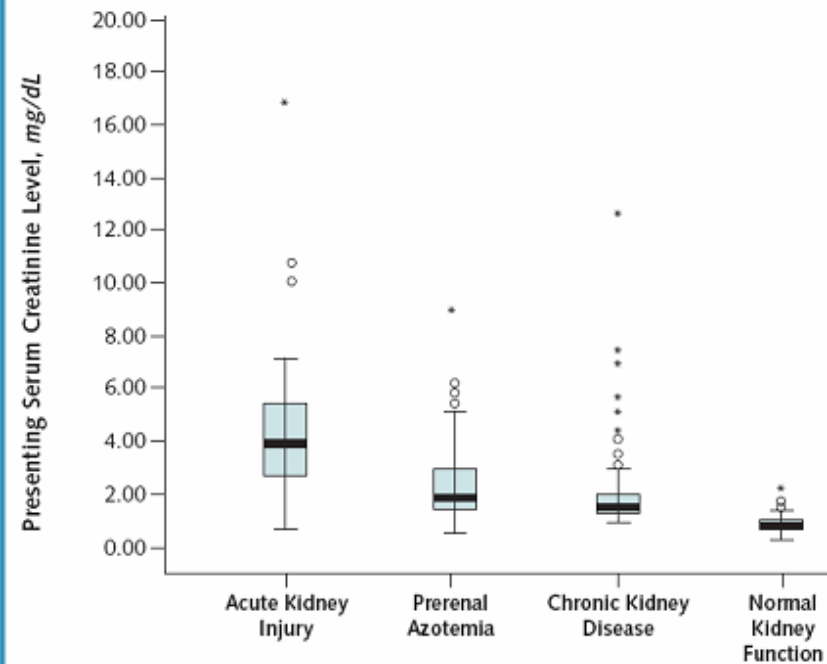
NGAL in the Emergency Department

Urine NGAL by diagnostic group



Patients with AKI have markedly elevated mean uNGAL levels when compared with other forms of kidney dysfunction.

sCr by diagnostic group



Patients with AKI had significantly elevated sCr compared with other forms of kidney dysfunction, but there was considerable overlap.

Conclusions of Nickolas et al.

- “A single measurement of urinary NGAL helps to distinguish acute kidney injury from normal function, prerenal azotemia, and chronic kidney disease, and predicts poor outcomes.”
- “... urinary NGAL level identifies acute kidney injury in a broad patient sample with different mechanisms of injury.”
- “... urinary NGAL level remained highly diagnostic even when the timing of injury was unknown, making NGAL potentially diagnostic of kidney disease for many clinical presentations.”

Summary and conclusions

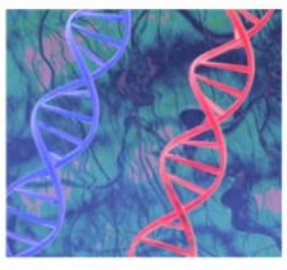
- Acute kidney injury (AKI) is a common medical problem associated with dramatic increased cost of care, and significant morbidity and mortality.
- Current clinical practice relies on an increase in serum creatinine to diagnose AKI – however this approach lacks specificity, and is not useful for early diagnosis.
- NGAL is one of the earliest proteins induced in the kidney after ischemic or nephrotoxic insult, and NGAL is easily detected in the urine soon after AKI.

Summary and conclusions (continued)

- Many studies have shown that urine NGAL is an early marker of kidney injury in a wide variety of settings.
- Larger prospective (validation) studies are underway to further define the role of urine NGAL in the early diagnosis, risk stratification, and prognosis of acute kidney injury.
- Application of urine NGAL testing has the potential to improve patient outcomes and reduce the financial burden of AKI.

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



Thank You