

Acute Kidney Injury: Diagnosis Using Novel Biomarkers

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AKI 2010, Edmonton

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Conflict of Interest

- I have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
- Affiliation/Financial Interest: Consultant, Honorarium, Licensing of NGAL technology
- Name of Organization(s): Abbott Diagnostics and Biosite, Inc.

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Educational Objectives

1. Discuss the importance of distinguishing early structural versus late functional AKI biomarkers
2. Discuss roles and applications of structural injury biomarkers in AKI
3. Discuss promising examples of structural injury biomarkers in AKI

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Structural versus Functional Injury

Biomarker	AMI	AKI
Functional (assess response)	End organ perfusion Ejection fraction Cardiac Index	Serum creatinine Urine output Serum cystatin C
Structural (initiate therapies)	Troponins CPK-MB Myoglobin	Urine sediment (for established AKI)

Need early structural biomarkers for timely treatment of AKI

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Previous randomized AKI trials

- Anaritide in AKI
Allgren et al
NEJM 1997
- IGF-I in AKI
Hirschberg et al
Kidney Int 1999

Double blind, placebo-controlled

No improvement in primary outcome

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Previous randomized AKI trials

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Kidney Int 1999

Double blind, placebo-controlled

No improvement in primary outcome

SCr ~ 4.5 at enrollment!

SCr ~ 7.0 at enrollment!

Akin to waiting for the onset of cardiogenic shock before intervening in AMI

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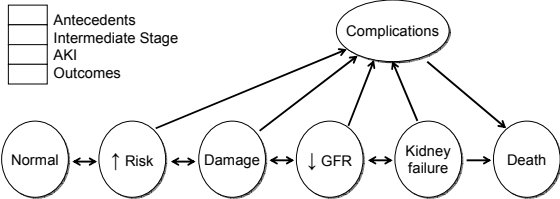
Interventions that prevent AKI in animals

Paradigm	Before Injury	Soon After Injury
Vasodilators	Diuretics, Mannitol, Dopamine, Calcium Channel Blocker, Endothelin Antag	ACE inhibitor, ANP, Phosphodiesterase inhibitor, BNP, Endothelin Antag
Growth Factors	IGF-1, EGF, HGF, NGAL	IGF-1, NGAL
Antioxidants/ Anti-inflammatory	N-acetylcysteine, P-selectin Antag	ICAM-1 antibody, Alpha-MSH

The paucity of early biomarkers has crippled our ability to institute timely therapy in humans

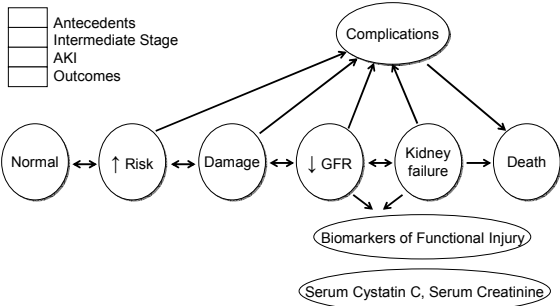
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Clinical Continuum of AKI

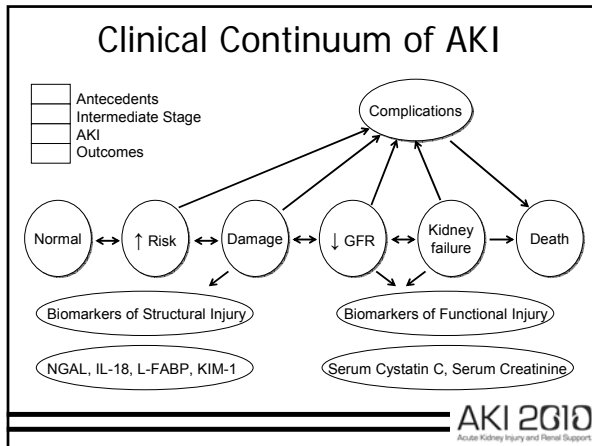


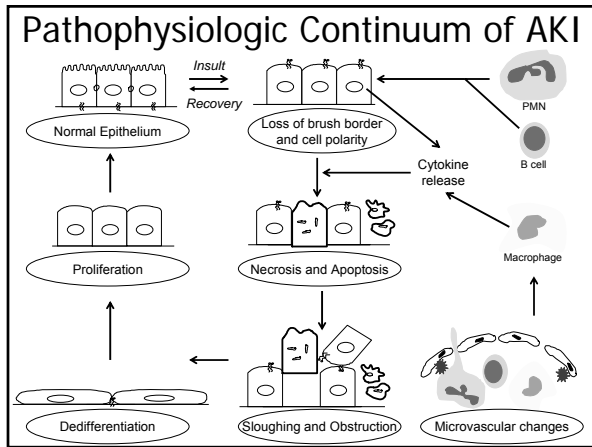
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What Can AKI Biomarkers Teach Us?

- Early prediction and diagnosis of AKI (before increase in serum creatinine)
 - Risk stratification
 - Early initiation of current therapies
 - Enrollment criteria for future therapies

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What Can AKI Biomarkers Teach Us?

- Pinpoint the type (pre-renal, AKI, CKD), duration and severity of acute kidney injury
- Identify the primary etiology of AKI (ischemic, septic, toxic, combination)
- Predict clinical outcomes (dialysis, death, length of hospital stay)
- Monitor response to intervention and treatment

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Human AKI Biomarkers Currently Under Investigation

- NGAL (urine and plasma)
 - KIM-1 (urine)
 - L-FABP (urine)
 - IL-18 (urine)
 - Cystatin C (urine and plasma)
 - GST α and π (urine)
 - GGTP (urine)
 - Beta 2-microglobulin (urine)
- } *Novel
Validating*
- } *Established
Retesting*

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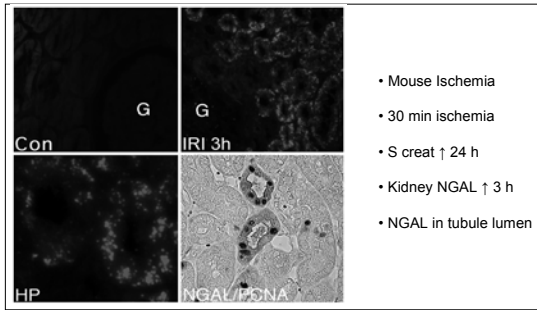
NGAL: Discovery Phase

- Neutrophil gelatinase-associated lipocalin
- Normally very small amounts in kidney tubules
- One of the most upregulated genes in the kidney by gene expression profiling, soon after ischemic or nephrotoxic AKI
- Protein product highly over-expressed in the kidney, during early phases of AKI

Supavekin et al, *Kidney Int* 63:1714-24, 2003 (ischemia)
Kieran et al, *Kidney Int* 64:480-492, 2003 (ischemia)
Amin et al, *Environ Health Perspect* 112:465-479, 2004 (cisplatin)
Yuen et al, *Physiol Genomics* 25:375-386, 2006 (ischemia & HgCl)
Hung Y-C et al, *Food Chem Toxicol* 45:1123-1130, 2007 (cisplatin)
Grigoryev et al, *J Am Soc Nephrol* Jan 30, 2008 (ischemia)

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Discovery: Kidney NGAL in Ischemic AKI

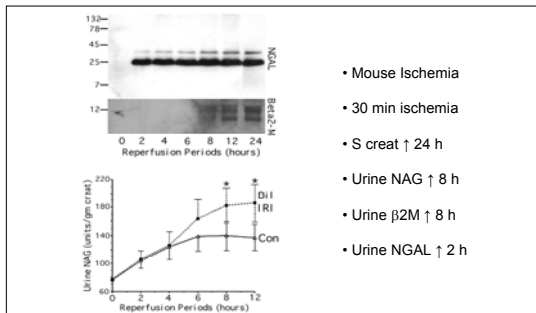


- Mouse Ischemia
- 30 min ischemia
- S creat \uparrow 24 h
- Kidney NGAL \uparrow 3 h
- NGAL in tubule lumen

Mishra et al, JASN 14:2534-43, 2003

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Discovery: Urine NGAL in Ischemic AKI



- Mouse Ischemia
- 30 min ischemia
- S creat \uparrow 24 h
- Urine NAG \uparrow 8 h
- Urine β 2M \uparrow 8 h
- Urine NGAL \uparrow 2 h

Mishra et al, JASN 14:2534-43, 2003

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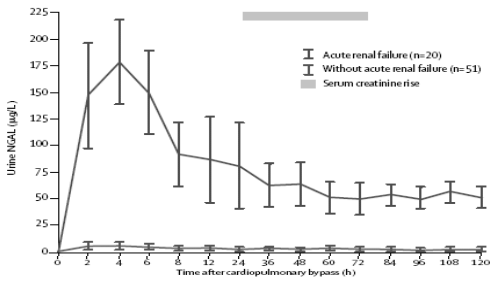
Phase 2 Transition: Human NGAL ELISA

- Sandwich monoclonal ELISA for human NGAL
- Inter- and intra-assay coefficient variations 5%
- Ready for initial human trials

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

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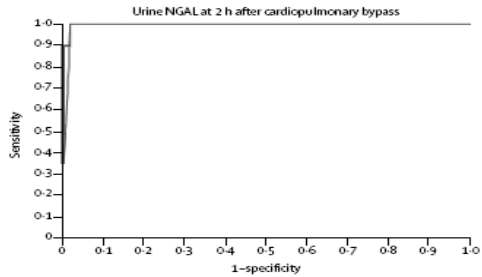
Phase 2: Urine NGAL (ELISA) as an Early AKI Biomarker after CPB



AKI = 50% or greater increase in serum creatinine from baseline
Mishra et al, Lancet 2005, 365:1231-1238



Phase 2: Urine NGAL (ELISA) as an Early AKI Biomarker after CPB



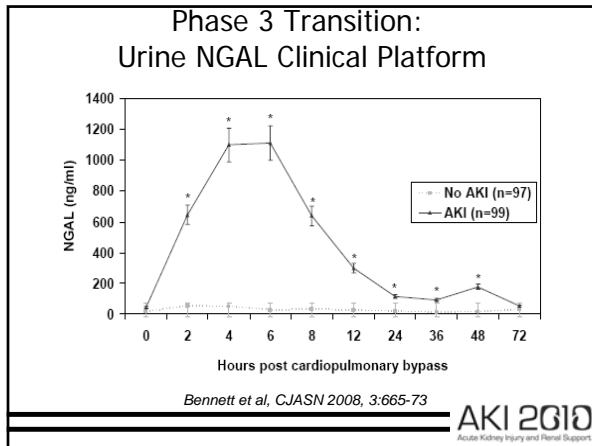
For 2 hour urine NGAL, AUC = 0.99 for prediction of AKI
Mishra et al, Lancet 2005, 365:1231-1238



Phase 3 Transition:
Urine NGAL Clinical Platform

- NGAL Immunoassay* for automated clinical platform
- Coefficient of variation < 5.0%
- Results in < 30 minutes with 150 µl urine





Phase 3 Transition: Urine NGAL Clinical Platform

*Using the 2 hr Urine NGAL measured by
Clinical Platform for prediction of AKI*

Sensitivity 80%
Specificity 92%
ROC AUC 0.95

Bennett et al, CJASN 2008, 3:665-73

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Phase 2/3: NGAL as a Biomarker for the Early Diagnosis of Human AKI

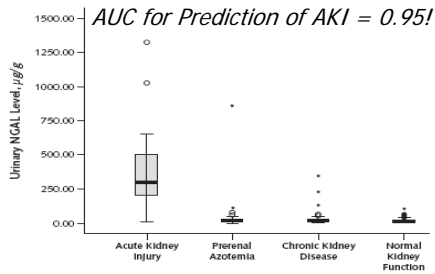
Biomarker Name	Cardiopulmonary Bypass (CPB)	Contrast induced Nephropathy	Sepsis/ICU or ED Setting	Kidney Transplant (tx)
NGAL	2 hr post CPB 2 days pre AKI	2 hr post contrast 1-2 days pre AKI	2 days pre AKI	12 hr post tx 2-3 days pre DGF
ROC AUC (ref)	0.8 (1-9)	0.88	0.85	0.90

*AKI = 50% or greater increase in serum creatinine from baseline
1154 subjects, 304 events*

(1) Mishra et al, Lancet 2005, 365:1231-8 (U+P: n=71; AKI=20; AUC 0.91-0.99)
 (2) Wagener et al, Anesthesiol 2006, 105: 485-91 (U: n=81; AKI=16; AUC 0.78)
 (3) Portilla et al, KI 2008, 4:465-72 (U: n=40; AKI=20; AUC 1.0)
 (4) Parikh et al, KI 2006, 70:199-203 (U: n=55; AKI=20; AUC 0.95)
 (5) Koyner et al, KI 2008, 74:1059-69 (U: n=72; AKI=34; AUC 0.71)
 (6) Xin et al, Ren Fail 2008, 30:904-13 (U: n=33; AKI=9; High S/S)
 (7) Dent et al, Crit Care 2007, 11(6):R127 (P: n=120; AKI=45; AUC 0.96)
 (8) Bennett et al, CJASN 2008, 3:665-73 (U: n=196; AKI=99; AUC 0.95)
 (9) Wagener et al, AJKD 2008, 52:425-33 (U: n=426; AKI=85; AUC 0.61)

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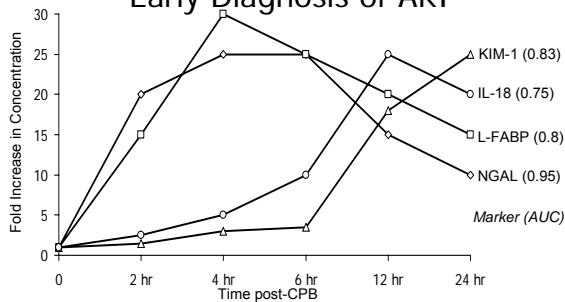
NGAL as an Early Biomarker of AKI in an Unselected Heterogeneous Setting



Nickolas et al, *Ann Int Med* 2008, 148:810-19

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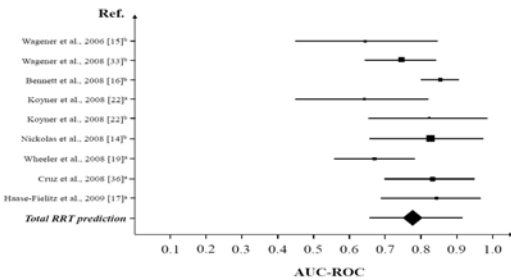
Sequential Urinary Biomarkers for Early Diagnosis of AKI



NGAL: Mishra, *Lancet* 2005, 365:1231-1238; L-FABP: Portilla, *KI* 2008, 4:465-72
KIM-1: Han, *KI* 2008, 7:863-9; IL-18: Parikh, *KI* 2006, 70:199-203

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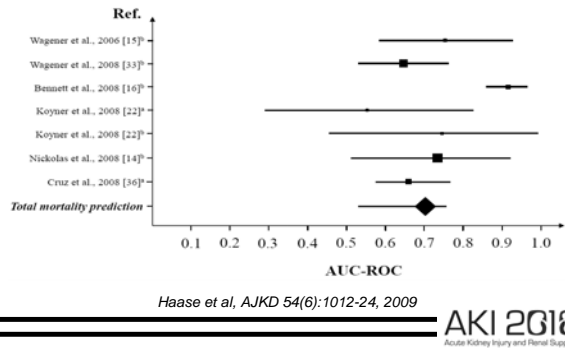
Early NGAL Measurements Predict Subsequent Need For Dialysis



Haase et al, *AJKD* 54(6):1012-24, 2009

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Early NGAL Measurements Predict In-hospital Mortality in AKI



Clinical Scenario: Year 2011

- Patient presents to ED with h/o nausea, vomiting
- Appears ill, HR 130/min, BP 90/60 mmHg
- Serum creatinine normal
- Admitted to ICU
- At high risk for developing AKI
- What should you do next, to predict AKI?

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Clinical Scenario: Year 2011

- Patient presents to ED with h/o nausea, vomiting
- Appears ill, HR 130/min, BP 90/60 mmHg
- Serum creatinine normal
- What should you do next, to predict AKI?

Check the NGAL level!

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Clinical Scenario: Year 2011

- Patient presents to ED with h/o nausea, vomiting
- Appears ill, HR 130/min, BP 90/60 mmHg
- Serum creatinine normal, admitted to ICU

NGAL level	Diagnosis	Intervention
<100 ng/ml	No AKI	Routine care



Clinical Scenario: Year 2011

- Patient presents to ED with h/o nausea, vomiting
- Appears ill, HR 130/min, BP 90/60 mmHg
- Serum creatinine normal, admitted to ICU

NGAL level	Diagnosis	Intervention
<100 ng/ml	No renal injury	Routine care
>150 ng/ml	High risk for AKI	? ANP/BNP ? Fenoldepam ? Bicarbonate ? Early dialysis ? Other



Other Responses to Early Biomarkers

Be Warned, Be Watchful

- Monitor intensively
- Monitor fluid balance, urine output
- Monitor blood pressure, cardiac function
- Monitor electrolytes, kidney function



Other Responses to Early Biomarkers

Do No Harm

- Avoid and treat hypotension
- Avoid and treat hypovolemia
- Avoid and treat oliguria
- Avoid contrast agents
- Avoid nephrotoxic medications

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Other Responses to Early Biomarkers

Early Intervention with dialysis

- Early fluid overload
- Cytokine removal in sepsis
- Toxin removal after contrast administration

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Clinical Scenario: Year 2011

- Patient presents to ED with h/o nausea, vomiting
- Appears ill, HR 130/min, BP 90/60 mmHg
- Serum creatinine normal, admitted to ICU

NGAL level	Diagnosis	Intervention
<100 ng/ml	No renal injury	Routine care
150-300 ng/ml	High risk for AKI	? ANP/BNP ? Fenoldepam ? Bicarbonate ? Early dialysis
Very high	High risk for AKI, dialysis and death	Start dialysis

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Summary

1. Serum creatinine is a delayed functional AKI biomarker
2. Better structural biomarkers of AKI such as NGAL, KIM-1, IL-18, and L-FABP are now available
3. Early NGAL measurements predict subsequent development of AKI
4. Early NGAL measurements predict subsequent dialysis requirement and death in patients with AKI
5. Early NGAL measurements provide a window of opportunity to intervene in AKI, and hold promise for changing the outcome of patients with AKI

Thank you for your attention!

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