Biomarkers of Progression to CKD

Giuseppe Castellano, MD, PhD
University of Bari,
Dept of Emergency and Organ Transplantation
AKI quality care in a continuity

AKI in the Community
Risk modification, prevention, monitoring

Acute Kidney Disease
Follow-up and prevention of CKD and recurrent AKI

AKI Prevention in the Hospital
Risk modification, prevention, monitoring

Renal Replacement Therapy
Optimizing outcome

AKI Management in the Hospital
Treatment and optimizing outcomes

Kianoush Kashani et al. CJASN doi:10.2215/CJN.01250119
What are the clinical complications of AKI?

Risk of Chronic Dialysis and Death Following Acute Kidney Injury

Ron Wald, MDCM, a,b Robert R. Quinn, MD, c Neill K. Adhikari, MDCM, d Karen E. Burns, MD, b,c Jan O. Friedrich, MD, b,c Amit X. Garg, MD, e Ziv Harel, MD, f Michelle A. Hladunewich, MD, g,h Jin Luo, MD, i Muhammad Mammadli, PharmD, a,i Jeffrev Perl, MD, a,i Joel G. Rav. MD a,i: for the University of Toronto Acute Kidney Injury Research Group

In a population based study of hospitalised patients with severe AKI-requiring dialysis, the risk of new ESRD was increased by three-fold.

Bellomo R, Intensive Care Med 2017

Recovery from AKI

- Early Recovery
  - AKI
    - Stage 1
    - Stage 2
    - Stage 3
  - Up to 7 Days Post Injury

- AKD
  - 7-90 Days Post Injury

- CKD
  - >90 Days Post Injury

Long-term survival in patients with septic acute kidney injury is strongly influenced by renal recovery

Marco Fiorentino\textsuperscript{1,2}*, Fadi A. Tohme\textsuperscript{1,3,4}, Shu Wang\textsuperscript{1,5}, Raghavan Murugan\textsuperscript{1,3}, Derek C. Angus\textsuperscript{3}, John A. Kellum\textsuperscript{1,3,4}*

Fig 2. Kaplan-Meier survival curves stratified by recovery status. The three groups are significantly different overall, $p < 0.001$ (Peto-Peto-Prentice test).
Increased risk of death and *de novo* chronic kidney disease following reversible acute kidney injury

Ion D. Bucaloiu¹, H. Lester Kirchner², Evan R. Norfolk¹, James E. Hartle II¹ and Robert M. Perkins¹,³

¹Department of Nephrology, Geisinger Medical Center, Danville, Pennsylvania, USA; ²Biostatistics and Research Data Core, Center for Health Research, Geisinger Medical Center, Danville, Pennsylvania, USA and ³Center for Health Research, Geisinger Medical Center, Danville, Pennsylvania, USA

**Table 4** Cox proportional hazard for time to death and *de novo* CKD (recovered AKI vs. controls)

<table>
<thead>
<tr>
<th></th>
<th>Death HR (95% CI)</th>
<th>De novo CKD HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted for index hospital length-of-stay</td>
<td>1.48 (1.19, 1.82)</td>
<td>1.91 (1.75, 2.09)</td>
</tr>
<tr>
<td>Adjusted for index hospital length-of-stay and <em>de novo</em> CKD</td>
<td>1.18 (0.95, 1.46)</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Abbreviations: AKI, hospital-associated acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio.*
AKI and CKD are not separate entities: a continuum of disease

- AKI: an abrupt decrease in kidney function occurring over 7 days or less,
- CKD is defined by the persistence of kidney disease for a period of >90 days;
- AKD describes acute or subacute damage and/or loss of kidney function for a duration of between 7 and 90 days after exposure to an AKI initiating event;
- Recovery from AKI within 48h of the initiating event typically heralds rapid reversal of AKI.
- Patients who suffer AKD with pre-existing CKD are probably at high-risk of kidney disease progression

Adapted from Chawla, L. S. et al. Nat. Rev. Nephrol. 2017
AKI 2-3 during hospital admission

Assess Discharge Renal Function*

Advanced Renal Dysfunction?

Yes

Nephrology referral and regular monitoring as clinically indicated

No

Hospital Follow-up

Stable Renal Function?

Yes

CKD Stage 4-5

Review at one Year

No CKD

Treat according to baseline-risk

Stable CKD Stage 1-3

Primary Care Follow-up

AKI follow-up 3 months after discharge*

* Assessment of renal function at discharge and follow-up includes measurement of serum creatinine, urinalysis and consideration of additional tests including creatinine clearance, serum cystatin c or measured GFR, particularly in survivors of critical illness when muscle mass and creatinine generation are likely to be abnormal.
Acute Kidney Disease (3 months)

Highly Susceptible Kidney
(Baseline GFR > 90 ml/min and RFR < 30 ml/min) or Established CKD

Biomarker Domain (Subclinical)

Increased Risk Acute Kidney Stress (AKS)

Acute Kidney Injury (AKI with Damage)

Acute Kidney Injury (AKI with dysfunction)

Creatinine Domain (sCr KDIGO Clinical)

Kidney Recovery (GFR > 60 ml/min)

Organ Death Dialysis

CKD (GFR < 60 ml/min)

Normal Kidney
Normal Baseline GFR and intact RFR (>30 ml/min)

Recovery Patterns:
- a) Early sustained reversal
- b) Late reversal
- c) Relapsing AKI with recovery
- d) Relapsing AKI without recovery
- e) Non reversal

Full Recovery
(Baseline GFR > 90 ml/min and RFR > 30 ml/min)

Adaptive Repair

Maladaptive Repair

Sclerosis Fibrosis

Partial Recovery (GFR < 60 ml/min)

Ronco AJRCCM 2017
Acute kidney injury

- Cell cycle arrest
- Infiltration of inflammatory cells
- Stimulation of fibrocytes & myofibroblasts
- Secretion of inflammatory cytokines

Glomerular hyperfiltration
Mitochondrial dysfunction
Reduced capillary density
Pericyte proliferation
Secretion of proinflammatory factors
Collagen deposition
Tubulo-interstitial fibrosis

Risk factors
- Race or ethnic group
- Older age
- Genetic factors
- Comorbidities: hypertension
  - Diabetes mellitus
  - Cardiac disease
  - Chronic kidney disease
- Type and severity of acute disease
- Severity and duration of AKI

Recovery

Chronic kidney disease

Complement-mediated endothelial dysfunction in I/R injury

T24h ctr

T24h C1-INH

Curci C., Castellano G. Nephrol Dial Transplant. 2014
C5a drives Perycicle to Myofibroblast Transdifferentiation in AKI

Castellano G, Franzin R et al, Frontiers in Immunology 2018
The prevalence of CKD is increasing worldwide and consequently the risks for renal replacement therapies, such as dialysis and transplantation and the incidence of cardiovascular events are also increasing.

Therefore there is an urgent need to identify novel and efficient biomarkers for predicting the decline of glomerular filtration rate (GFR) and the progression of renal disease, as well as to provide tools for more efficient treatments for patients with CKD.

[The United States Renal Data System. 2016 USRDS Annual Data Report: Epidemiology of Kidney Disease 2016]

[Jha V, Lancet 2013]
What is a biomarker?

“a characteristics that is objectively measured and evaluated as an indicator of normal biological process, pathogenic process, or pharmacologic response to a therapeutic intervention”.

<table>
<thead>
<tr>
<th>Test</th>
<th>Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height</td>
<td>Growth</td>
</tr>
<tr>
<td>Urinary dipsticks for nitrites</td>
<td>UTI</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Disease severity in IgA nephropathy.</td>
</tr>
<tr>
<td>Anti-GBM Ab</td>
<td>Good pastures syndrome (anti-glomerular basement membrane disease)</td>
</tr>
</tbody>
</table>
Ideal Biomarker

- Non – invasive
- Easily obtainable
- Measurable using standardized assays
- Fast results
- Cost
Kidney Biomarkers

> 20 protein biomarkers have been intensively studied:

- Urinary biomarkers are: non invasive, easy to measure, easily obtainable and provide earlier detection.

- Urinary biomarkers many be classified as those of structural injury or functional injury.
Candidate Biomarkers for Kidney Injury

Proximal Tubules
- KIM-1
- L-FABP
- Albumin
- Clusterin
- Lipocalin (NGAL)
  - GSTα
  - β2-microglobulin
  - α1-microglobulin
  - NAG
  - Osteopontin
  - Cystatin C
  - Netrin-1
- IL-18
  - Retinol binding prot
  - HGF, NHE-3
  - Cyr61
  - Exosomal Fetuin-A
  - TIMP2
  - IGFBP7

Distal Tubules
- Osteopontin
- Clusterin
- Lipocalin (NGAL)
  - GST-μ/π
  - NAG
  - EGF
  - Osteopontin
  - Cystatin C
  - IL-18
  - Calbindin-D28

Loop of Henle
- Osteopontin

Collecting Duct
- Calbindin- D28

Glomerulus
- Creatinine
- Cystatin C
- Protein, albumin
- Podocalyxin
- β2-microglobulin
- WT-1 in exosomes

Bonventre et al. Nature Biotech 2010
# Biomarkers of functional injury

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Functionation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystatin C*</td>
<td>Glomerular injury; in urine indicates proximal tubule injury</td>
</tr>
<tr>
<td>Total protein β2-microglobulin albumin</td>
<td>Glomerular and tubular dysfunction</td>
</tr>
<tr>
<td>Brush border antigens</td>
<td></td>
</tr>
<tr>
<td>Adenosine deaminase binding protein</td>
<td></td>
</tr>
<tr>
<td>Carbonic anhydrase</td>
<td>Proximal tubule injury</td>
</tr>
<tr>
<td>Other tubular antigens</td>
<td></td>
</tr>
<tr>
<td>Urinary enzymes</td>
<td></td>
</tr>
<tr>
<td>N-acetyl-β-D-glucosaminidase</td>
<td></td>
</tr>
<tr>
<td>Alanine aminopeptidase</td>
<td></td>
</tr>
<tr>
<td>Cathepsin B</td>
<td>Proximal tubule injury</td>
</tr>
<tr>
<td>γ-glutamyltransferase</td>
<td></td>
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<tr>
<td>α-glutathione-S-transferase</td>
<td></td>
</tr>
<tr>
<td>β-glucosidase</td>
<td>Proximal tubule &gt; distal tubule injury</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td></td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>Distal tubule &gt; proximal tubule injury</td>
</tr>
<tr>
<td>Type of biomarkers</td>
<td>Selective sites and associated types of injury</td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Kidney injury molecule-1 (KIM-1)*</td>
<td>Proximal tubule injury (Ischemic AKI, nephrotoxins, RCC)</td>
</tr>
<tr>
<td>n-acetyl glucosaminidase (NAG)</td>
<td>Proximal tubule injury</td>
</tr>
<tr>
<td>Neutrophil gelatinase-associated lipocalin (NGAL)*</td>
<td>Tubule and collecting duct injury (Ischemic AKI, nephrotoxins, delay allograft renal function)</td>
</tr>
<tr>
<td>Interleukin (IL)-18*</td>
<td>Tubule injury (AKI, delayed allograft renal function)</td>
</tr>
<tr>
<td>Clusterin</td>
<td>Tubule injury</td>
</tr>
</tbody>
</table>
Currently, the diagnosis of CKD is made usually on the levels of blood urea and serum creatinine (sCr).
Limitations of serum creatinine
## Limitations of serum creatinine

<table>
<thead>
<tr>
<th>Disease</th>
<th>Limitations of serum creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI and CKD</td>
<td>Nonspecific to disease etiology</td>
</tr>
<tr>
<td></td>
<td>Delayed marker of kidney damage</td>
</tr>
<tr>
<td></td>
<td>Dependent on clinical characteristics (age, sex, muscle mass, etc.)</td>
</tr>
<tr>
<td></td>
<td>Insensitive to small changes in GFR</td>
</tr>
<tr>
<td>AKI</td>
<td>Dependent on hemodynamic steady state</td>
</tr>
<tr>
<td></td>
<td>Altered in hospitalized patients (i.e., by diuretics, IV fluids)</td>
</tr>
<tr>
<td></td>
<td>Assay-related interference (i.e., by bilirubin)</td>
</tr>
<tr>
<td>CKD</td>
<td>Unchanged despite kidney damage in tubulointerstitial and vascular disease</td>
</tr>
<tr>
<td></td>
<td>May be falsely low with significant proteinuria</td>
</tr>
<tr>
<td></td>
<td>Provides imprecise eGFR estimations</td>
</tr>
<tr>
<td></td>
<td>Requires special considerations for eGFR equations with changing muscle mass (i.e., in children, cirrhotics)</td>
</tr>
</tbody>
</table>

William R. Zhang, Annual Review of Physiology 2019
Albuminuria is the classic sensitive marker of early renal dysfunction but excludes many patients that will only have proteinuria when GFR is already significantly decreased.

Albuminuria is also utilized as a marker of risk for CKD progression.

However, strategies that decrease albuminuria do not always prevent the progression of kidney disease.
New emerging biomarker in the diagnosis of CKD and in the prediction of outcome

- KIM-1
- NGAL
- TIMP2-IGFBP7
- ASYMMETRIC DIMETHYLARGININE (ADMA)
- Symmetric Dimethylarginine (SDMA)
- Uromodulin
- β2M beta-2 microglobulin
- miRNA, ncRNA, IncRNA
- Metabolic biomarkers
### Table 2 Biomarkers of short-term acute kidney injury (AKI) recovery versus persistence to acute kidney disease (AKD)

<table>
<thead>
<tr>
<th>AKI biomarker</th>
<th>Characteristics</th>
<th>Clinical setting</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensinogen</td>
<td>453 amino acid protein; precursor of angiotensin I</td>
<td>Acute CRS, Cardiac surgery, ICU</td>
<td>AKI progression</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>13 kDa cysteine protease inhibitor produced by all nucleated human cells; undergoes glomerular filtration</td>
<td>ICU</td>
<td>RRT</td>
</tr>
<tr>
<td>Hepatocyte growth factor</td>
<td>Antifibrotic cytokine produced by mesenchymal cells and involved in tubular cell regeneration after AKI</td>
<td>ICU</td>
<td>RRT</td>
</tr>
<tr>
<td>IGFBP7</td>
<td>29 kDa and 21 kDa proteins involved in cell cycle arrest; released into urine after tubular cell stress</td>
<td>ICU, Cardiac surgery</td>
<td>RRT</td>
</tr>
<tr>
<td>TIMP-2</td>
<td>18 kDa pro-inflammatory cytokine; regulates innate and adaptive immunity; released into urine after proximal tubular cell injury</td>
<td>ICU, Acute CRS, Cardiac surgery, Renal transplantation</td>
<td>RRT, DGF</td>
</tr>
<tr>
<td>IL-18</td>
<td>18 kDa transmembrane glycoprotein involved in tubular regeneration; released into urine following ischemic or nephrotoxic tubular cell damage</td>
<td>ICU, Hospitalised patients</td>
<td>RRT, Need for RRT, DGF</td>
</tr>
<tr>
<td>KIM-1</td>
<td>39 kDa intracellular lipid chaperone produced in proximal tubular cells; aids in regulation of fatty acid uptake and intracellular transport; excretion into urine after tubular injury</td>
<td>ICU, Cardiac surgery</td>
<td>AKI progression</td>
</tr>
<tr>
<td>L-FABP</td>
<td>14 kDa intracellular lipid chaperone produced in proximal tubular cells; aids in regulation of fatty acid uptake and intracellular transport; excretion into urine after tubular injury</td>
<td>ICU, Cardiac surgery</td>
<td>AKI progression</td>
</tr>
<tr>
<td>MicroRNA</td>
<td>Endogenous single-stranded molecules of non-coding nucleotides; upregulated following tubular cell injury and cell proliferation; detectable in plasma and urine</td>
<td>ICU, Cardiac surgery</td>
<td>AKI progression</td>
</tr>
<tr>
<td>NAG</td>
<td>&gt;130 kDa lysosomal enzyme; produced in proximal and distal tubular cells; released into urine after tubular cell injury</td>
<td>Hospitalised patients</td>
<td>RRT</td>
</tr>
<tr>
<td>NGAL</td>
<td>At least three different types: Monomeric 25 kDa glycoprotein produced by neutrophils and epithelial cells, including renal tubules; Homodimeric 45 kDa protein produced by neutrophils; Heterodimeric 135 kDa protein produced by renal tubular cells released into urine following systemic production or tubular injury</td>
<td>ICU, Cardiac surgery, Acute CRS, Renal transplantation</td>
<td>AKI progression</td>
</tr>
</tbody>
</table>

Relevant references are mentioned in the text

AKI acute kidney injury, CRS cardiorenal syndrome, DGF delayed graft function, ICU intensive care unit, IGFBP-7 insulin-like growth factor binding protein 7, IL-18 interleukin 18, L-FABP liver-type fatty acid-binding protein, KIM-1 kidney injury molecule-1, NAG N-acetyl-β-D-glucosaminidase, NGAL neutrophil gelatinase-associated lipocalin, TIMP-2 tissue metalloproteinase 2, RRT renal replacement therapy, kDa kilodalton
Tubular localization of CKD biomarkers

Proximal tubular injury: NGAL, KIM-1, TIMP-2, IGFBP-7

Proximal tubular function: CysC, α1M, L-FABP

Distal tubule injury: NGAL

Loop of Henle injury: UMOD

Inflammation: IL-18, IL-6, IL-10, TNFR1, TNFR2

Repair and fibrosis: MCP-1, YKL-40, PIINP, EGF
Kidney Injury Molecule-1 (KIM-1)

- Preclinical data have also demonstrated that KIM-1 is **upregulated in the later phases of AKI** and is believed to play an important role in renal repair.

- Higher urinary KIM-1 associated with worse outcome in **established AKI**.

References:
- Hubank M, Schatz DG. 1994
- Prozialeck WC, Kidney Int. 2008
KIM-1 and tubule interstitial damage

Kim-1 expression was limited to areas with inflammation and fibrosis (α-smooth muscle actin)
Neutrophil gelatinase – associated lipocalin (NGAL)

- Predominantly found in proliferating nuclear antigen–positive proximal tubule cells.

- Most consistent biomarkers found during AKI to CKD transition.

- Also predicts development of DGF.
ASYMMETRIC DIMETHYLARGININE (ADMA)

- ADMA is considered to be the “missing link” between cardiovascular disease and CKD
- Is an endogenous inhibitors of nitric oxide synthases.
- Higher ADMA levels hamper the generation of endothelial nitric oxide and promote the development of endothelial dysfunction and hypertension in CKD.
- ADMA impairs endothelial function by diminishing arterial endothelial nitric oxide synthase (eNOS) phosphorylation via the inhibition of Ca/calmodulin-dependent protein kinase CaMKII.

Ueda, S. et al Nephrology 2007

Asymmetric dimethylarginine (ADMA) as an important risk factor for the increased cardiovascular diseases and heart failure in chronic kidney disease

Xiaohong Liu, Xin Xu, Ruru Shang, Yingjie Chen

*VIP Department, Shanxi Provincial People's Hospital, Taiyuan, China
*Department of Exercise Rehabilitation, Shanghai University of Sport, Shanghai, 200430, China
Cardiovacular Division and Lillehei Heart Institute, University of Minnesota, Minneapolis, MN55455, USA
Uromodulin

Proximal tubular injury: NGAL, KIM-1, TIMP-2, IGFBP-7

Proximal tubular function: CysC, α1M, L-FABP

Distal tubule injury: NGAL

Inflammation: IL-18, IL-6, IL-10, TNFR1, TNFR2

Repair and fibrosis: MCP-1, YKL-40, PIINP, EGF

Loop of Henle injury: UMOD

Proximal tubule

Distal convoluted tubule

Collecting duct

Glomerulus

Loop of Henle
Uromodulin

- Uromodulin (UMOD) is an 85-kDa glycoprotein exclusively produced by cells of the thick ascending limb of Henle.

- Studies in animal models and clinical settings have demonstrated its ability to serve as a biomarker for tubular mass and function and accordingly, UMOD has been shown to be inversely associated with many kidney disease states:
  - a marker for the number of remaining functional tubules.

SteuBID, et al. Medicine 95,2016. :e3011
New emerging biomarkers in the diagnosis of CKD and in the prediction of outcome

- KIM-1
- NGAL
- TIMP2-IGFBP7
- ASYMMETRIC DIMETHYLARGININE (ADMA)
- Symmetric Dimethylarginine (SDMA)
- Uromodulin
- β2M beta-2 microglobulin
- miRNA, ncRNA, IncRNA
- Metabolomic biomarkers
Proteomic and Metabolomic Biomarkers

• 287 disease-specific biomarkers for focal segmental glomerulosclerosis (FSGS)

• 291 for minimal change disease (MCD)

• 311 for membranous nephropathy (MN)

• 172 for lupus nephritis (LN)

• 509 for renal vasculitis

• 116 for IgA nephropathy (IgAN)

• 619 diabetic nephropathy and nephrosclerosis (DN&N)-specific biomarker

Proteomic and Metabolomic Biomarkers

• In a majority of CKD types, altered abundance of collagen fragments has been observed

• Urinary collagen fragments are early biomarkers for CKD (in patients with GFR > 60 mL/min/1.73 m2)

• However, they are not good markers in more advanced stages

Cell cycle Regulators and Wnt-beta Catenin signalling in AKI

Castellano G, Franzin et al, Under Review
Both IGFBP-7 (through p523 and p21) and TIMP-2 (through p27) block the effect of cyclin-dependent protein kinase complexes and cause short periods of G1 cell-cycle arrest.

These biomarkers were originally discovered in the clinical setting of critical illness and have been approved by the FDA for use in conjunction with clinical evaluation in intensive care unit patients who have acute cardiovascular and/or respiratory compromise.

Boonstra J, Post JA. Gene 2004
TIMP-2 /IGFBP-7

Kashani k, Critical CARE 2013
Endothelial dysfunction and microvascular rarefaction
  • renal hypoxia
  • ↓ nitric oxide production
  • EndMT
  • Pericyte-myofibroblast transition

Incomplete regeneration of tubular cells
  • EMT
  • G2/M cell cycle arrest and ↑ production of pro-fibrotic factors (TGF-β, CTGF)

Persistent chronic inflammation
  • switch M1→ M2 macrophage phenotype
  • ↑ complement cascade
  • Adaptive immune system response

Mitochondrial dysfunction

Epigenetic modifications
  • DNA methylation
  • histone changes
  • expression of specific microRNA

RAS activation
  • ↑ urinary angiotensinogen as AKI-to-CKD biomarker

Cell and tissue senescence
  • activation of pro-senescent molecules (p21, p16/NK4α)
  • ↓ α-Klotho levels

Fiorentino et al. Contrib Nephrol 2018
Epigenetic mechanisms are implicated in the AKI-to-CKD progression

Epigenetics: The heritable mechanisms that control gene expression without changes in DNA sequence.

Christina M. Wyatt, KI 2018
C5a induces significant alterations in methylation profile

C5a induced a whole chromosomes hypomethylation

Castellano G, Franzin et al, Under Review
Klotho modulation during experimental AKI and DGF

Swine model of I/R injury
I/R injury causes a reduction in renal Klotho expression in a Complement-dependent manner

Transplant Patients
Patients with DGF develop a persistent deficiency in local and systemic production of soluble Klotho

Biomarker integrated model of AKI

Schematic for AKI/AKD follow-up.

- **Stage 1 AKI of Short Duration (1 day)**
  - SCr normal or returns to baseline
  - Hospital Limited Event in healthy pt
  - Consider RAMPS/bundle within 1 year

- **Duration of Stage 1 AKI (1-2 days)**
  - Limited Co-morbidities
  - No prior CKD
  - SCr not returning to baseline
  - Consider RAMPS in 6 months

- **Prolonged Stage 1 AKI (3-6 days) or Stage 2 AKI for shorter duration (1-3 days)**
  - Increasing co-morbidities (advancing age,)
  - SCr persistently elevated < 25% of pre-existing baseline
  - Labs in the next 3-6 weeks with long term RAMPS/neph appt (next several months)

- **Prolonged Stage 2 AKI with UA showing injury (duration ≥ 7 days)**
  - Multiple co-morbidities (cancer, prior AKIs, mild CKD at baseline)
  - SCr persistently elevated > 25% above prior baseline in some but some recovery
  - Labs in 1-2 weeks w/neph appt / RAMPS in weeks

- **Stage 3 AKI and Persistent other forms of AKI or kidney disease**
  - History of Prior AKI, significant CV dx, hypertension, diabetes mellitus and advanced CKD
  - Labs within days of discharge and follow up with Nephrology-RAMPS within 1 week

- **AKI-D recovered and non-recovered**
  - Prior CKD 4
  - Recurrent AKI/AKD
  - RAMPS or WATCH ME
  - Labs within days of discharge and follow up with Nephrology within 1 week

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Kianoush Kashani et al. CJASN doi:10.2215/CJN.01250119
After an episode of AKI?

• Serial follow-up measurements of:
  • sCreatinine, Creatinine clearance, sCystatin C

• Proteinuria:
  • strongly associated with cardiovascular risk and progression of CKD at all levels of GFR

• Biomarkers of Tubulo-Interstitial:
  • Inflammation
  • Senescence
  • Fibrosis

New Therapies
Art is I, Science is We
THANK YOU

Giuseppe Castellano, MD, PhD
University of Bari, Dept of Emergency and Organ Transplantation