Scratching the Surface: “Subclinical” Acute Kidney Injury

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Critical Care Canada Forum
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Objectives

Discuss/Understand:

1. Scope of the problem of AKI
2. Diagnostic/classification in AKI
3. Subclinical AKI
Acute Kidney Injury is a COMMON and SERIOUS PROBLEM
Research

RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis

Eric AJ Hoste\textsuperscript{1,2}, Gilles Clermont\textsuperscript{1}, Alexander Kersten\textsuperscript{1}, Ramesh Venkataraman\textsuperscript{1}, Derek C Angus\textsuperscript{1}, Dirk De Bacquer\textsuperscript{3} and John A Kellum\textsuperscript{1}

Incidence \textasciitilde 67\%; Worsening AKI \textasciitilde 56\%
• 91,254 admissions to 20 Australian ICUs (‘96-’05)
• Incidence 5.2% ~ ↑ rate by 2.8% per year
Demographic Transition in AKI

- Advancing age
- ↑ Co-morbid disease
- ↑ CKD prevalence
- ↑ Diagnostic procedures
- ↑ Complex procedures
- ↑ Advanced technology
- ↑ Illness severity
- ↑ Multi-organ support

- Complex cardiac Sx
- LVAD/RVAD
- TAP/BImpella/ECMO
- TAVI
- Cardiac/lung Tx
- Liver/kidney/pancreas
- SCT/BMT
- Immune suppression

AKI is increasingly **multi-factorial and multi-insult**
Mortality in Severe AKI

![Bar chart showing mortality and incidence in different studies: Brivet (64%), Guerin (71%), Metnitz (63%), Ostermann (62%), Bagshaw (60%), BEST (62%), Cruz (50%), Delamoy (52%).](chart.png)

- **Mortality (%)**:
  - Brivet: 64%
  - Guerin: 71%
  - Metnitz: 63%
  - Ostermann: 62%
  - Bagshaw: 60%
  - BEST: 62%
  - Cruz: 50%
  - Delamoy: 52%

- **Incidence (%)**:
  - Brivet: 50%
  - Guerin: 52%

Legend:
- **Yellow Bar**: Morality
- **Red Line**: Incidence
The severity of acute kidney injury predicts progression to chronic kidney disease

Lakhmir S. Chawla\textsuperscript{1,2}, Richard L. Amdur\textsuperscript{3,4}, Susan Amodeo\textsuperscript{3,5}, Paul L. Kimmel\textsuperscript{1,6} and Carlos E. Palant\textsuperscript{1,3}

\textbf{Independent factors:} ↑ age, diabetes mellitus, ↓ albumin, ↓ hemoglobin, severity 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,e Jan O. Friedrich, MD, b,e Amit X. Garg, MD, f Ziv Harel, MD, a Michelle A. Hladunewich, MD, d,g Jin Luo, MD, h Muhammad Mamdani, PharmD, b,i Jeffrey Perl, MD, o,b Joel G. Ray, MD b,j; for the University of Toronto Acute Kidney Injury Research Group

Adj-HR 3.23; 95% CI, 2.70-3.86
Adj-HR 2.70; 95% CI, 2.42-3.00
Predictors of Health Utility among 60-Day Survivors of Acute Kidney Injury in the Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network Study

Kirsten L. Johansen,* Mark W. Smith,†‡ Mark L. Unruh,§ Andrew M. Siroka,† Theresa Z. O’Connor,¶ and Paul M. Palevsky,**†† for the VA/NIH Acute Renal Failure Trial Network

27% HUI equal to or worse than death

HUI 0.40 (±0.37) (mean [SD])
How Do We Currently DEFINE AKI?

AKI is an abrupt and sustained decline in kidney function and represents a complex syndrome that occurs in a broad spectrum of settings, with clinical manifestations ranging from a minimal elevation in serum creatinine to overt anuric renal failure.
### AKI - The challenge...

<table>
<thead>
<tr>
<th>SCR Δ 8.8 µmol/L</th>
<th>72 hr ΔSCR ≥25 µmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCR ≥44.2 µmol/L</td>
<td>72 hr ΔSCR ≥44.2 µmol/L</td>
</tr>
<tr>
<td>SCR ≥150 µmol/L</td>
<td>72 hr ΔSCR ≥50 µmol/L</td>
</tr>
<tr>
<td>SCR ≥177 µmol/L</td>
<td>72 hr ΔSCR ≥100 µmol/L</td>
</tr>
<tr>
<td>SCR ≥186 µmol/L and 2x increase</td>
<td>MDRD GFR: ΔCrCl ≥50%</td>
</tr>
<tr>
<td>SCR ≥177 µmol/L and Δ ≥ 62 µmol/L</td>
<td>Cockcroft-Gault GFR: 72hr ΔCrCl &lt;15%</td>
</tr>
<tr>
<td>SCR ≥200 µmol/L</td>
<td>Cockcroft-Gault GFR: 72hr ΔCrCl &lt;25%</td>
</tr>
<tr>
<td>SCR ≥283 µmol/L or 2x increase</td>
<td>Cockcroft-Gault GFR: 72hr ΔCrCl &lt;50%</td>
</tr>
<tr>
<td>SCR ≥442 µmol/L</td>
<td>Urine α1-/β2-microglobulin, NAG, NGAL</td>
</tr>
<tr>
<td>SCR ≥25%</td>
<td>Urine Output &lt;100mL/8hr</td>
</tr>
<tr>
<td>SCR ≥50%</td>
<td>Require RRT</td>
</tr>
<tr>
<td>SCR ≥100%</td>
<td>RIFLE/AKIN criteria.......</td>
</tr>
</tbody>
</table>

Hoste et al IJAO 2008
AKI - The consequence...

Chertow et al. JASN 2005
2.1.1: AKI is defined as any of the following (Not Graded):
- Increase in SCr by \( \geq 0.3 \text{ mg/dl} \ (\geq 26.5 \text{ \(\mu\text{mol/l}\)}) \) within 48 hours; or
- Increase in SCr to \( \geq 1.5 \) times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume \( < 0.5 \text{ ml/kg/h} \) for 6 hours.

2.1.2: AKI is staged for severity according to the following criteria (Table 2). (Not Graded)

Table 2 | Staging of AKI

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum creatinine</th>
<th>Urine output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5–1.9 times baseline OR ( \geq 0.3 \text{ mg/dl} \ (\geq 26.5 \text{ (\mu\text{mol/l})}) ) increase</td>
<td>(&lt; 0.5 \text{ ml/kg/h for 6–12 hours})</td>
</tr>
<tr>
<td>2</td>
<td>2.0–2.9 times baseline</td>
<td>(&lt; 0.5 \text{ ml/kg/h for } \geq 12 \text{ hours})</td>
</tr>
<tr>
<td>3</td>
<td>3.0 times baseline OR Increase in serum creatinine to ( \geq 4.0 \text{ mg/dl} \ (\geq 353.6 \text{ (\mu\text{mol/l})}) ) OR Initiation of renal replacement therapy OR In patients (&lt; 18) years, decrease in eGFR to (&lt; 35 \text{ ml/min per 1.73 m}^2)</td>
<td>(&lt; 0.3 \text{ ml/kg/h for } \geq 24 \text{ hours}) OR Anuria for ( \geq 12 \text{ hours})</td>
</tr>
</tbody>
</table>
Our Consensus Definitions for AKI are Imperfect!

• We still make a “late” diagnosis
• We need to know a baseline creatinine
• We know urine output ≠ correlate with SCr
• *We cannot segregate aspects of “damage” (i.e. type, onset, propagation, recovery) from “decrements in function”*
Creatinine is NOT an Ideal Marker of AKI!

• sCr is the current gold standard
• sCr (normal range) varies widely by age/sex, diet, muscle, drugs, and fluid status…
• sCr can take > 24 hr to a new steady state
• > 50% of kidney function may be lost before a significant ↑ in sCr is detected
Real-Time, Bedside GFR

3ml IV injection of large & small fluorescent marker

Small marker filtered across glomerulus, large marker retained in vascular space
Candidate Novel AKI Biomarkers

CysC
NGAL
KIM-1
γ-GT
IL-18
L-FABP
NAG
Hepcidin
etc…
What Can AKI Biomarkers Tell Us?

**DIAGNOSIS -**
- Early detection of “structural” damage – preceding “functional” decline
- Aid in discriminating etiology and severity:
  - Reversible vs. established vs. CKD

**CLINICAL ACTIONS -**
- Risk stratification for “renal protection”
- Triage decision-making
- Early initiation/discontinuation of interventions
- Enrollment criteria for future therapies
Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery

Jaya Mishra*, Catherine Dent*, Ridwan Tarabishi*, Mark M Mitsnefes, Qing Ma, Caitlin Kelly, Stacey M Ruff, Kamyar Zahedi, Mingyuan Shao, Judy Bean, Kiyoshi Mori, Jonathan Barasch, Prasad Devarajan

Urine NGAL 2 hr post CPB: AuROC 0.998

Acute renal failure (n=20)
Without acute renal failure (n=51)
Serum creatinine rise

Mishra et al Lancet 2005

Thomas L. Nickolas, MD, MS; Matthew J. O’Rourke, BS; Jun Yang, MD, PhD; Meghan E. Sise, BS; Pietro A. Canetta, MD; Nicholas Barasch, BS; Charles Buchen; Faris Khan, MD; Kiyoshi Mori, MD, PhD; James Giglio, MD; Prasad Devarajan, MD; and Jonathan Barasch, MD, PhD

Diagnosis of AKI ~ NGAL >130 µg/g
Sensitivity 0.90 (0.73-0.98)
Specificity 0.99 (0.99-1.00)

n=635, AKI defined according to RIFLE criteria
n=1635, AKI defined according to RIFLE criteria; Events = RRT or in-hospital death
Neutrophil Gelatinase—Associated Lipocalin Predicts Acute Kidney Injury in Patients Undergoing Liver Transplantation

Andrew J. Portal,1 Mark J. W. McPhail,1,3 Matthew Bruce,1 Iona Coltart,1 Andrew Slack,1 Roy Sherwood,2 Nigel D. Heaton,1 Debbie Shawcross,1 Julia A. Wendon,1 and Michael A. Heneghan1

Plasma NGAL

Urine NGAL

APACHE II ~ OR 1.64 (1.22-2.21; p=0.001; AUC 0.87)
pNGAL ~ OR 1.01 (1.00-1.02; p=0.002; AUC = 0.87)

“Renal Risk Score" using APACHE II > 13 and pNGAL >258 ng/mL showing 100% sensitivity and 76% specificity for severe AKI

n=95
Prospective observational study of 632 consecutive ICU patients, 171 (27.1%) developed AKI (RIFLE criteria) in first ICU week – admission p/u NGAL

AuROC  0.77  0.80  0.86

AuROC  0.80  0.85  0.88

Plasma NGAL

Urine NGAL
Neutrophil Gelatinase-associated Lipocalin at ICU Admission Predicts for Acute Kidney Injury in Adult Patients

Hilde R. H. de Geus¹, Jan Bakker¹, Emmanuel M. E. H. Lesaffre²,³, and Jos L. M. L. le Noble¹

¹Department of Intensive Care and ²Department of Biostatistics, Erasmus University Medical Center, Rotterdam, The Netherlands; and ³LiBiostat, Catholic University of Leuven, Leuven, Belgium

<table>
<thead>
<tr>
<th>AuROC</th>
<th>N (%)</th>
<th>Plasma NGAL</th>
<th>Urine NGAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=632)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RRT in 1st week</td>
<td>28 (4.4)</td>
<td>0.88</td>
<td>0.89</td>
</tr>
<tr>
<td>Hospital Mortality</td>
<td>137 (21.7)</td>
<td>0.63</td>
<td>0.64</td>
</tr>
</tbody>
</table>

- Admission urine/plasma NGAL predict AKI severity
- Accuracy improved with worsening RIFLE category (F > I > R)
- Urine/plasma NGAL predict AKI severity better than sCr or eGFR
- Admission urine/plasma NGAL improved the accuracy of the most efficient “clinical model” and results in improved net reclassification
What is “Subclinical AKI”? 

• What is it?  
• How do we diagnose it?  
• Does it matter?
The Outcome of Neutrophil Gelatinase-Associated Lipocalin-Positive Subclinical Acute Kidney Injury

A Multicenter Pooled Analysis of Prospective Studies

Ngal (+)/sCr(-) 19.2%
New Paradigm for the Spectrum of AKI

(NOAKI)
sCr (negative)
NGAL (negative)

(STRUCTURAL AKI)
sCr (negative)
NGAL (positive)

(FUNCTIONAL AKI)
sCr (positive)
NGAL (negative)

(AKI (BOTH))
sCr (positive)
NGAL (positive)
The Outcome of Neutrophil Gelatinase-Associated Lipocalin-Positive Subclinical Acute Kidney Injury

A Multicenter Pooled Analysis of Prospective Studies
Diagnostic and Prognostic Stratification in the Emergency Department Using Urinary Biomarkers of Nephron Damage

A Multicenter Prospective Cohort Study

<table>
<thead>
<tr>
<th>sCr (mg/dl)</th>
<th>&lt;1.4</th>
<th>≥1.4</th>
<th>n.s.</th>
</tr>
</thead>
<tbody>
<tr>
<td>uNGAL (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;104</td>
<td>(n=227)</td>
<td>(n=236)</td>
<td>(n=174)</td>
</tr>
<tr>
<td>low risk</td>
<td>intermediate risk</td>
<td>high risk</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>sCr (mg/dl)</th>
<th>&lt;1.4</th>
<th>≥1.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>uKIM-1 (ng/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2.82</td>
<td>(n=264)</td>
<td>(n=264)</td>
</tr>
<tr>
<td>low risk</td>
<td>intermediate risk</td>
<td>high risk</td>
</tr>
</tbody>
</table>

A: Event rates (%)

B: Event rates (%)
Subclinical AKI – Does It Matter?

- ↑ Risk of progression to overt AKI
- ↑ Risk for need for RRT
- ↑ Risk of death
- ↑ Risk of future ESKD
- ↑ Risk of new CKD
- Surrogate of illness severity (↑ non-renal organ damage)
Can NGAL coupled with BNP risk stratify after discharge?

- **Design:** Multi-centre study
  - 186 adults ADHF
- **Interventions:** Serial measures of BNP, NGAL
- **Outcomes:** Readmission and/or death at 30 and 90-d (event rate 15.6%)
Discharge levels of markers

Maisal et al Eur J Heart Fail 2011
Prognostic utility of plasma neutrophil gelatinase-associated lipocalin in patients with acute heart failure: The NGAL EvaLuation Along with B-type NaTriuretic Peptide in acutely decompensated heart failure (GALLANT) trial

<table>
<thead>
<tr>
<th>Group</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGAL &lt;100, BNP &lt;330</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>NGAL &lt;100, BNP &gt;330</td>
<td>3.23</td>
<td>0.3</td>
</tr>
<tr>
<td>NGAL &gt;100, BNP &lt;330</td>
<td>9.95</td>
<td>0.04</td>
</tr>
<tr>
<td>NGAL &gt;100, BNP &gt;330</td>
<td>16.85</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Subclinical AKI ~ Summary

- AKI is common/increasing
- AKI portends ↑ risk for worse outcomes
- New kidney-damage specific biomarkers represent novel tools for diagnostics
- Biomarker-only defined AKI – new paradigm – identifying a novel vulnerable subgroup
Acknowledgements

Prasad Devarajan
Michael Haase
Rinaldo Bellomo
Mink Chawla