New perspectives in Acute Kidney Injury

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  • Dynamed, Goldilocks Ther, Reata, Angion, Alpha Young
• Review Panels:
  • NIH, Department of Veterans Affairs
Acute Kidney Injury
(Acute Renal Failure)
The Blitz, London, 1941
CRUSH INJURIES WITH IMPAIRMENT OF RENAL FUNCTION

BY

E. G. L. BYWATERS, M.B., B.S., M.R.C.P.

Beit Memorial Fellow

AND

D. BEALL, Ph.D., Toronto

(From the Departments of Medicine and Pathology, British Postgraduate Medical School)

[WITH SPECIAL PLATE]
Evolving Definition and Classification of AKI

AKI proposed

September 2004: The term AKI is proposed to reflect the entire spectrum of ARF

ARF described

ARF is described by E.G. Bywaters in his observations of patients after crush injuries from the London bombings in WWII

AKIN classification of AKI

AKIN develops uniform standards for defining and classifying AKI

RIFLE staging for ARF

May 2004: To address the lack of a consensus definition for ARF, the ADQI devises the RIFLE definition and staging system for ARF

KDIGO unifies definitions of AKI

Kidney Disease: Improving Global Outcomes (KDIGO) recognizes the need for a single unifying definition of AKI using RIFLE and AKIN criteria as the basis

References:
Diagnosis and Staging of AKI

<table>
<thead>
<tr>
<th>Creatinine*</th>
<th>Urine output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Rise of ≥26 μmol/L within 48 h or 50–99% rise from baseline within 7 days†</td>
</tr>
<tr>
<td>Stage 2</td>
<td>100–199% rise from baseline within 7 days†</td>
</tr>
<tr>
<td>Stage 3</td>
<td>≥200% rise from baseline within 7 days†; or concentration ≥354 μmol/L, with either: rise of ≥26 μmol/L within 48 h or ≥50% rise from baseline within 7 days†; or any requirement for renal replacement therapy</td>
</tr>
<tr>
<td></td>
<td>&lt;0.5 mL/kg per h for more than 6 h</td>
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<tr>
<td></td>
<td>&lt;0.5 mL/kg per h for more than 12 h</td>
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<tr>
<td></td>
<td>&lt;0.3 mL/kg per h for 24 h or anuria for 12 h</td>
</tr>
</tbody>
</table>

*Creatinine and urine output are defined as follows: 

†Anuria is defined as urine output less than 0.5 mL/kg per h for more than 6 h. 

Table 1: The KDIGO classification system®
AKI is on the rise and a growing threat

- Increases length of stay (3.5 days)
- Increases health care utilization ($5.4 to $24.0 billion)
- With dialysis, cost increases from $11,016 to $42,077 per hospitalization

Silver and Chertow, Nephron 2017
What can we learn about dialysis dependent acute kidney injury from the USRDS?

USRDS
United States Renal Data System
2005-2014

Mortality HR compared to DM
0-3 months
1.28
(1.24-1.32)
3-6 months
1.16
(1.11-1.20)

Recovery of kidney function
Most (95%) recoveries were within 12 months

Lower likelihood of recovery
Woman
Blacks, Asians, Hispanics, Native Americans

1,045,540 incident dialysis patients
32,598 (3%) incident dialysis due to AKI
11,498 (35%) recovery

Conclusions
Kidney failure due to AKI confers a higher risk of mortality in the first 6 months compared to kidney failure due to diabetes. Recovery within 12 months is common, though less so among women, Black, Asian, Hispanic, and Native American patients.


Silvi Shah et al. CJASN 2020;15:995-1006
AKI in Hospitalized Patients with COVID-19

Lili Chan,¹,²,³,⁴ Kumardeep Chaudhary,³,⁴,⁵ Aparna Saha,³,⁴ Kinsuk Chauhan,¹ Akhil Vaid,⁶ Shan Zhao,⁶,⁷ Ishan Paranjpe,⁶ Sulaiman Somani,⁶ Felix Richter,⁵,⁶ Riccardo Miotto,⁵,⁶ Anuradha Lala,⁷,⁸ Arash Kia,⁹,¹⁰ Prem Timsina,⁹,¹⁰ Li Li,⁵,¹¹ Robert Freeman,¹² Rong Chen,⁵,¹¹ Jagat Narula,¹²,¹³ Allan C. Just,¹⁴ Carol Horowitz,²,⁹ Zahi Fayad,¹⁵,¹⁶ Carlos Cordon-Cardo,¹⁷ Eric Schadt,⁵,¹¹ Matthew A. Levin,⁷ David L. Reich,⁷ Valentin Fuster,⁸ Barbara Murphy,¹,² John C. He,¹,² Alexander W. Charney,⁵,¹⁸,¹⁹ Erwin P. Böttinger,⁶,²⁰ Benjamin S. Glicksberg,⁵,⁶ Steven G. Coca,¹,² and Girish N. Nadkarni,¹,²,³,⁴,⁶ on behalf of the Mount Sinai COVID Informatics Center (MSCIC)*
Acute Kidney Injury in Hospitalized Patients with COVID-19

Proportion of AKI and outcomes of AKI

5 MSHS Hospitals

Feb 27 → May 30

3993 hospitalized patients with COVID-19

AKI (N=3993) AKI-D in AKI (N=1835) Death in AKI (N=1835)
Lower survival in COVID-19 and AKI

Chan et al, J Am Soc Nephrol 2021
Clinical productivity for Nephrology

A Daily hospital admissions

Clinical productivity for Nephrology

Clinical productivity for Nephrology

Daily CRRT treatments

AKI: Long-term Outcomes
Risk of Progressive Chronic Kidney Disease (Stage 4 or Higher) after AKI

- 562,799 patients with GFR ≥45 ml/min/1.73m² before hospitalization

Lowell J. Lo et al. Risk of Progressive Chronic Kidney Disease after AKI
Kidney Outcomes in Long COVID

Benjamin Bowe, Yan Xie, Evan Xu and Ziyad Al-Aly
Kidney Outcomes in Long COVID

Benjamin Bowe, Yan Xie, Evan Xu and Ziyad Al-Aly

<table>
<thead>
<tr>
<th>Incident rate</th>
<th>Excess burden/1000 person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-hospitalized</td>
<td>2.52</td>
</tr>
<tr>
<td>Hospitalized no AKI</td>
<td>5.68</td>
</tr>
<tr>
<td>Hospitalized with AKI</td>
<td>49.99</td>
</tr>
</tbody>
</table>

Hazard ratio

1.83 (1.43, 2.34)
2.66 (1.72, 4.12)
8.98 (6.03, 13.37)

2021, In press
Utilization of deep learning for subphenotype identification in sepsis-associated AKI

Methods and Cohort:
- EHR data from ICUs in a tertiary care hospital
- Adult patients with sepsis and AKI within 48h of ICU admission
- Deep learning utilizing all available vital signs, labs, and comorbidities
- K Means clustering to identify subphenotypes

Patients with sepsis and AKI:
- N=4001
  - Subphenotype 1: N=1443
  - Subphenotype 2: N=1898
  - Subphenotype 3: N=660

Chaudhary et al, CJASN 2020
Utilization of deep learning for subphenotype identification in sepsis-associated AKI

Chaudhary et al, CJASN 2020
Large differences on dialysis and mortality across AKI subphenotypes
Biomarkers
Proximal tubules
- Kim-1
- Clusterin
- NGAL
- GST-α
- β2-microglobulin
- α1-microglobulin
- NAG
- Osteopontin
- Cystatin C (urinary)
- Netrin-1
- RBP
- IL-18
- HGF
- Cyr61
- NHE-3
- Exosomial fetuin-A
- L-FABP
- Albumin

Distal tubules
- Osteopontin
- Clusterin
- GST-μ/π
- NGAL
- H-FABP
- Calbindin D28

Collecting duct
- Calbindin D28

Loop of Henle
- Osteopontin
- NHE-3

Glomerulus
- Total protein
- Cystatin C (urinary)
- β2-microglobulin
- α1-microglobulin
- Albumin

Bonventre *Nature Biotech* 28(5), 2010
Soluble Urokinase Receptor and Acute Kidney Injury

Salim S. Hayek, M.D., David E. Leaf, M.D., Ayman Samman Tahhan, M.D., Mohamad Raad, M.D., Shreyak Sharma, M.B., B.S., Sushrut S. Waikar, M.D., M.P.H., Sanja Sever, Ph.D., Alex Camacho, Ph.D., Xuexiang Wang, M.D., Ph.D., Ranadheer R. Dande, M.D., Nasrien E. Ibrahim, M.D., Rebecca M. Baron, M.D., Mehmet M. Altintas, Ph.D., Changli Wei, M.D., Ph.D., David Sheikh-Hamad, M.D., Jenny S.-C. Pan, M.D., Michael W. Holliday, Jr., M.D., Ph.D., James L. Januzzi, M.D., Steven D. Weisbord, M.D., Arshed A. Quyyumi, M.D., and Jochen Reiser, M.D., Ph.D.
suPAR

Soluble urokinase plasminogen activator receptor

- Circulating form of a glycosyl-phosphatidylinositol–anchored three-domain membrane protein
- Very low basal levels in cells such as endothelial cells, podocytes
- Levels are strongly predictive of progressive decline in kidney function in proteinuric kidney diseases

Wei et al. Nature Medicine 2011
Risk Prediction for Acute Kidney Injury — Super Important, Now suPAR Easy?

Frank Tacke, M.D., Ph.D.
A  Odds Ratio for Acute Kidney Injury after Angiogram

suPAR Quartiles (N=3827)

<table>
<thead>
<tr>
<th>Quartile 1</th>
<th>Reference</th>
<th>Quartile 2</th>
<th>1.85 (1.23–2.78)</th>
<th>P=0.003</th>
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<tbody>
<tr>
<td>Quartile 3</td>
<td>1.73 (1.15–2.61)</td>
<td>P=0.007</td>
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<tr>
<td>Quartile 3</td>
<td>2.04 (1.36–3.06)</td>
<td>P&lt;0.001</td>
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<tr>
<td>Quartile 4</td>
<td>3.14 (2.13–4.64)</td>
<td>P&lt;0.001</td>
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<tr>
<td>Quartile 4</td>
<td>3.79 (2.61–5.51)</td>
<td>P&lt;0.001</td>
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</tr>
</tbody>
</table>

Model 1

Model 2

Model 3
Plasma angiogenesis markers in AKI – TRIBE consortium

Vascular endothelial growth factor A
Placental growth factor
Soluble VEGF receptor 1

Mansour SG, AJKD 2019
Pathogenesis of AKI

- Hemodynamics
- Tubular injury and repair
- Role of Mitochondria
- Immune mechanisms
- Vascular endothelial injury
- Systemic & regional microcirculation
PGC1α drives NAD biosynthesis linking oxidative metabolism to renal protection

Mei T. Tran1,2, Zsuzsanna K. Zsengeller1,2,3, Anders H. Berg3,4, Eliyahu V. Khankin1,2, Manoj K. Bhasin2,5, Wondong Kim6, Clary B. Clish7, Isaac E. Stillman4, S. Ananth Karumanchi1,2,8, Eugene P. Rhee6,7 & Samir M. Parikh1,2
NAD+ metabolism

Fig. 1
Overview of NAD$^+$ metabolism
Nicotinamide Adenine Dinucleotide Biosynthetic Impairment and Urinary Metabolomic Alterations Observed in Hospitalized Adults With COVID-19–Related Acute Kidney Injury

Nathan H. Raines¹,¹¹, Matthew D. Cheung²,¹¹, Landon S. Wilson³, Jeffrey C. Edberg⁴, Nathaniel B. Erdmann⁵, Alec A. Schmaier⁶, Taylor F. Berryhill³, Zachary Manickas-Hill⁷, Jonathan Z. Li⁸, Xu G. Yu⁷, Anupam Agarwal², Stephen Barnes³,⁹ and Samir M. Parikh¹,¹⁰
De novo NAD\(^+\) biosynthetic impairment in acute kidney injury in humans

Ali Poyan Mehr\(^{1,12}\), Mei T. Tran\(^{1,12}\), Kenneth M. Ralto\(^{1,2,3,12}\), David E. Leaf\(^4\), Vaughan Washco\(^1\), Joseph Messmer\(^1\), Adam Lerner\(^5\), Ajay Kher\(^1\), Steven H. Kim\(^1\), Charbel C. Khoury\(^6\), Shoshana J. Herzig\(^7\), Mary E. Trovato\(^8\), Noemie Simon-Tillaux\(^1\), Matthew R. Lynch\(^1\), Ravi I. Thadhani\(^6\), Clary B. Clish\(^8,9\), Kamal R. Khabbaz\(^8,13\), Eugene P. Rhee\(^6,9,10\), Sushrut S. Waikar\(^4\), Anders H. Berg\(^7,13\) and Samir M. Parikh\(^{1,13}*\)
Oral NAD in cardiac surgery patients improves renal function

Fig. 4 | a

Day relative to surgery

\[ sCr (\text{mg dl}^{-1}) \]

\[ P = 0.01 \]

\[ \text{Placebo} \quad \text{1 g per day} \quad \text{3 g per day} \]

Meyr et al, Nature Med, Sept 2018
Macrophage - Dendritic Cell

D. Ferenbach and J. Hughes. Kidney Int. 74;5-7, 2008
Kidney network of mononuclear phagocytes

CX3CR1-expressing cells are intimately associated with the tubules.
Macrophages in AKI

- Depletion prior to ischemia-reperfusion decreases injury
- Depletion during repair phase delays recovery
The Kidney Contains Ontogenetically Distinct Dendritic Cell and Macrophage Subtypes throughout Development That Differ in Their Inflammatory Properties

Natallia Salei,1,2 Stephan Rambichler,1,2 Johanna Salvermoser,1,2 Nikos E. Papaioannou,1,2 Ronja Schuchert,3,4 Dalia Pakalniškytė,1,2 Na Li,5,6 Julian A. Marschner,6 Julia Lichtnekert,6 Christopher Stremmel,3,4 Filippo M. Cernilogar,7 Melanie Salvermoser,1,2 Barbara Walzog,1,2 Tobias Straub,8 Gunnar Schotta,7,9 Hans-Joachim Anders,6 Christian Schulz,3,4 and Barbara U. Schraml1,2
AKI: Long-term Outcomes

1 - Full Recovery
2 - AKI to CKD
3 - Acute-on-Chronic Kidney Disease
4 - AKI to ESRD

Renal Function vs. Time
Fate Tracing Reveals the Pericyte and Not Epithelial Origin of Myofibroblasts in Kidney Fibrosis

Benjamin D. Humphreys,* † Shuei-Liong Lin,**§
Akio Kobayashi,†¶ Thomas E. Hudson,* ‡
Brian T. Nowlin,* ‡ Joseph V. Bonventre,* †
M. Todd Valerius,†¶ Andrew P. McMahon,†¶
and Jeremy S. Duffield* ‡ ‡
Methylation in pericytes after acute injury promotes chronic kidney disease

Chou et al. J Clin Invest 2020
Bacterial sepsis triggers an antiviral response that causes translation shutdown

Takashi Hato, Bernhard Maier, Farooq Syed, Jered Myslinski, Amy Zollman, Zoya Plotkin, Michael T. Eadon, and Pierre C. Dagher

Kidney

Bacterial sepsis

PKR

eIF2α kinase

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Bacterial sepsis

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Bacterial sepsis

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Bacterial sepsis

PKR

eIF2α kinase

eIF2α
Treatment Strategies
## Interventions in AKI

<table>
<thead>
<tr>
<th>Drug</th>
<th>Biological rationale</th>
<th>Animal experiments</th>
<th>Uncontrolled human data</th>
<th>Small RCT</th>
<th>Large RCT</th>
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<td>Loop diuretics</td>
<td>Present</td>
<td>Favorable</td>
<td>Favorable</td>
<td>Negative</td>
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<td>Low-dose dopamine</td>
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<td>Favorable</td>
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<td>positive</td>
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</table>

The only FDA approved treatment of acute kidney injury is dialysis.

C. Ronco and R. Bellomo Nephron Clinical Practice 93:C13, 2003 (Slide from Mark Okusa)
Lactate is protective in sepsis-associated AKI
Lactate is protective in sepsis-associated AKI
Lactate Elicits ER-Mitochondrial Mg²⁺ Dynamics to Integrate Cellular Metabolism

Cassidy C. Daw,¹,²,⁵ Karthik Ramachandran,¹,²,⁵ Benjamin T. Enslow,¹,²,⁵ Soumya Maity,¹,² Brian Bursic,⁴ Matthew J. Novello,⁴ Cherubina S. Rubannelsonkumar,¹,² Ayah H. Mashal,¹,² Joel Ravichandran,¹,² Terry M. Bakewell,² Weiwei Wang,¹,² Kang Li,¹,² Travis R. Madaris,¹,² Christopher E. Shannon,² Luke Norton,² Soundarya Kandala,¹,² Jeffrey Caplan,³ Subramanya Srikantan,¹,² Peter B. Stathopoulos,⁴ W. Brian Reeves,¹,² and Muniswamy Madesh¹,²,⁶,*

¹Department of Medicine, Center for Precision Medicine, University of Texas Health San Antonio, San Antonio, TX 78229, USA
²Department of Medicine/Cardiology/Diabetes/Nephrology Divisions, University of Texas Health San Antonio, San Antonio, TX 78229, USA
³Department of Biological Sciences, Delaware Biotechnology Institute, University of Delaware, Newark, DE 19711, USA
⁴Department of Physiology and Pharmacology, Western University, London, ON N6A 5C1, Canada
Spotlight

O-Mg! Lactate Drives Mg$^{2+}$ Mobilization

Blake R. Wilde$^1$ and Heather R. Christofk$^{1,2,3,*}$
Renal Replacement Therapy

**Key Questions**

- *When should renal replacement therapy be initiated in AKI?*
- *Which modality is most appropriate?*
- *What is the appropriate dose of therapy?*
Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury

The STARRT-AKI Investigators, for the Canadian Critical Care Trials Group, the Australian and New Zealand Intensive Care Society Clinical Trials Group, the United Kingdom Critical Care Research Group, the Canadian Nephrology Trials Network, and the Irish Critical Care Trials Group*
Early initiation of RRT - higher risk of hypotension and hypophosphatemia
Hemodialysis in AKI
Dose of Dialysis

The Critically Ill Patient

- Continuous respiratory support
- Continuous nutritional support
- Continuous cardiac support
- Continuous renal support
- Enteral or parenteral feeding
- Cardiac monitoring, fluid/vasopressor therapy, pump assist
- Continuous neurological monitoring
- Ventilation by respirator
- CRRT

UAB MEDICINE
NEPHROLOGY
Post-hospital care for AKI survivors

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Caring for OutPatiEnts after Acute Kidney Injury (COPE-AKI) – Clinical Centers (U01 Clinical Trial Required)

Improving Care for Patients after Hospitalization with AKI

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PERSPECTIVES www.jasn.org

JASN 2020
Care coordination following AKI

- Nephrologists
- Patients recovering from AKI and critical illness
- Family members
- Other support
- Outpatient dialysis nurses and staff
- Primary care physicians
  - Rehabilitation physicians
  - Mental health personnel
  - Other specialists
- Social workers
  - Rehabilitation personnel
  - Dietitians
Kidney Precision Medicine Project (KPMP)

- Understand and treat human kidney disease
- Ethically and safely obtain kidney biopsies from participants with AKI or CKD
- Create a kidney tissue atlas
- Find disease subgroups to stratify patients
- Identify critical cells, pathways and targets for novel therapies
- Devise individualized treatments
- Improve scientific knowledge base
- Improve (young) investigator pipeline
Development of pharmacologic therapies for AKI and CKD has been hampered by:

- Animal models that fail to replicate the human disease phenotypes.
- The inability to identify and prioritize high value human targets.
- **Limited availability of human kidney biopsy tissue**
- Poor molecular understanding of human AKI and CKD heterogeneity.
Rationale and design of the Kidney Precision Medicine Project.

KPMP Kidney Biopsy

Study populations:
- Diabetes & CKD
- Hypertension & CKD
- Acute kidney injury

Clinical Presentation

Traditional & Digital Pathology
- CKD Progression
- Kidney Failure
- AKI
- Hospitalizations

Oomics & Imaging Integration

Clinical Outcomes

Create reference kidney tissue atlas

Develop mechanism-based disease subtypes

Identify critical cells, pathways, and targets for novel therapies

CONCLUSION:
The KPMP seeks to redefine and reclassify common kidney diseases by combining deep molecular phenotyping with clinical characteristics, innovative digital pathology, and clinical outcomes.

de Boer et al for the KPMP, 2020
KPMP Is Unique in Precision Medicine

- Patients, clinicians, scientists, ethicists – are included
- Patients are equitable partners with an active voice in the entire research enterprise
- The culture promotes priorities and safety of patients first
- Addresses the big public health problems in kidney diseases
- Clinical orientation of the kidney atlas
- Focus on kidney pathology and deep biological profiling
Summary and Conclusions

- AKI and AKI leading to CKD is a growing threat
- Recognition of subphenotypes of AKI – clinical implications
- Central role of mitochondria
- Immune mechanisms – resident macrophages
- CRRT preferred modality, although timing of intervention not clear
- Great potential for future developments
Thank you