THE CRISIS OF AKI FOLLOW-UP
KDIGO Controversies Conference of Acute Kidney Injury
Rome, Italy 4/19

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DISCLOSURES

• Honorarium: Invited educational talk at DaVita Annual Physician Conference 3/2019
• Royalties: Author for UptoDate
• Scientific Advisory: Editorial Board CJASN
• Consulting Agreement: Akebia Therapeutics
Conceptual Framework

GFR

AKI

Months

 AKI Hospitalization  Discharge  3  6  9  12

CKD/ESRD  CV Disease  Death  Disability  Poor Quality of Life

Conceptual Framework

AKI

KDIGO
2.3.4: Evaluate patients 3 months after AKI for resolution, new onset, or worsening of pre-existing CKD. (Not Graded)

- If patients have CKD, manage these patients as detailed in the KDOQI CKD Guideline (Guidelines 7–15). (Not Graded)
- If patients do not have CKD, consider them to be at increased risk for CKD and care for them as detailed in the KDOQI CKD Guideline 3 for patients at increased risk for CKD. (Not Graded)
## AKI Survivors vs Stable CKD: Apples and … Pears?

<table>
<thead>
<tr>
<th></th>
<th>Recent Hospitalized AKI</th>
<th>Stable CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced Comorbidity/ Burden</td>
<td>↑↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Acute Organ Dysfunction</td>
<td>↑↑↑</td>
<td>-</td>
</tr>
<tr>
<td>Potential for Ongoing Recovery</td>
<td>↑</td>
<td>-</td>
</tr>
<tr>
<td>Susceptibility to future injury/ rehospitalizations/mortality</td>
<td>↑↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Susceptibility to nephrotoxins and adverse drug events (ADEs)</td>
<td>↑↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Inadequate Solute/Fluid Intake</td>
<td>↑</td>
<td>-</td>
</tr>
<tr>
<td>Poor Quality of Life/Frailty</td>
<td>↑↑↑</td>
<td>↑</td>
</tr>
</tbody>
</table>
Kidney Surveillance after AKI

Serum Creatinine

Albuminuria/Proteinuria

Outpatient Nephrology Referral Among Patients with eGFR <60 ml/min/1.73 m² After AKI

KDIGO

44% Recovered/Improved
11.5% Died
8.5% Referred
36% None

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Siew et al. JASN 2012;23:305-312
# Identifying Patients at High Risk

**A** Point values for each variable

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Points</th>
</tr>
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<tbody>
<tr>
<td>&lt;50</td>
<td>0</td>
</tr>
<tr>
<td>50-59</td>
<td>1</td>
</tr>
<tr>
<td>60-69</td>
<td>2</td>
</tr>
<tr>
<td>70-79</td>
<td>2</td>
</tr>
<tr>
<td>80-89</td>
<td>2</td>
</tr>
<tr>
<td>≥90</td>
<td>3</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Acute kidney injury stage</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Discharge Scr, mg/dL</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.0</td>
<td>0</td>
</tr>
<tr>
<td>1.0-1.3</td>
<td>3</td>
</tr>
<tr>
<td>1.4-1.6</td>
<td>6</td>
</tr>
<tr>
<td>1.7-1.9</td>
<td>7</td>
</tr>
<tr>
<td>≥2.0</td>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>0</td>
</tr>
<tr>
<td>Women</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline Scr, mg/dL</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.6</td>
<td>0</td>
</tr>
<tr>
<td>0.6-0.7</td>
<td>1</td>
</tr>
<tr>
<td>0.7-0.8</td>
<td>1</td>
</tr>
<tr>
<td>0.8-0.9</td>
<td>2</td>
</tr>
<tr>
<td>0.9-1.0</td>
<td>2</td>
</tr>
<tr>
<td>1.0-1.1</td>
<td>3</td>
</tr>
<tr>
<td>1.1-1.2</td>
<td>3</td>
</tr>
<tr>
<td>1.2-1.3</td>
<td>4</td>
</tr>
<tr>
<td>≥1.3</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Albuminuria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>Mild</td>
<td>1</td>
</tr>
<tr>
<td>Heavy</td>
<td>3</td>
</tr>
<tr>
<td>Not measured</td>
<td>1</td>
</tr>
</tbody>
</table>

**B** Predicted risk of advanced chronic kidney disease

**Summation of Points:**

<table>
<thead>
<tr>
<th>Age</th>
<th>+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>+</td>
</tr>
<tr>
<td>Baseline serum creatinine value</td>
<td>+</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>+</td>
</tr>
<tr>
<td>Acute kidney injury stage</td>
<td>+</td>
</tr>
<tr>
<td>Discharge serum creatinine value</td>
<td>+</td>
</tr>
</tbody>
</table>

**Total Risk Score** =

<table>
<thead>
<tr>
<th>Total Risk Score</th>
<th>Predicted Risk of Advanced Chronic Kidney Disease, %</th>
<th>Percentage of Patients in Risk Category, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-8</td>
<td>&lt;1</td>
<td>Derivation Cohort: 44.0, External Validation Cohort: 45.0</td>
</tr>
<tr>
<td>9-14</td>
<td>1-5</td>
<td>Derivation Cohort: 43.6, External Validation Cohort: 43.8</td>
</tr>
<tr>
<td>15-17</td>
<td>5-10</td>
<td>Derivation Cohort: 7.2, External Validation Cohort: 7.1</td>
</tr>
<tr>
<td>18-19</td>
<td>10-20</td>
<td>Derivation Cohort: 2.5, External Validation Cohort: 2.1</td>
</tr>
<tr>
<td>≥20</td>
<td>≥20</td>
<td>Derivation Cohort: 2.7, External Validation Cohort: 2.0</td>
</tr>
</tbody>
</table>

James, MT et al. *JAMA* 2017; 318(19):1787-97
Disparity between Nephrologists' Opinions and Contemporary Practices for Follow-up after AKI Hospitalization.

A

Nephrologists' Opinions

- Recovery of kidney function
  - >80% above baseline
  - 20-60% above baseline
  - Full recovery

- Acute dialysis
  - No
  - Yes

- Heart failure
  - No
  - Yes

- Pre-existing CKD
  - No
  - Yes

- Age
  - ≥80 years
  - 70-79 years
  - 61-69 years
  - 60 years

B

Observed Practice

- Percentage, 95% CI

Divya J. Karsanji et al. CJASN 2017;12:1753-1761

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Nephrology Referral Associates with Improved Survival After Dialysis-Requiring AKI

(N=3877)

10.6/100 PY (19%)
8.4/100 PY (15%)

Is this Real?
What is Driving this?

HR 0.76 (95%CI:0.62-93)

Harel Kidney Int 2013; 83:901-08
Actionable Factors that may Modify Long-term Risk?
AKI Causes Salt Sensitivity of Blood Pressure, Predisposes to Proteinuria, and Loss of Autoregulation


Proteinuria May Worsen after AKI

Proportion of Patients by Proteinuria Level

Dipstick Proteinuria Concentration
- >3+
- 3+
- 2+
- 1+
- Trace
- Negative

OR for >= 1+ Proteinuria:
1.2-1.4

HYPERTENSION MAY BE A POTENTIAL MEDIATOR OF CV AND KIDNEY OUTCOMES FOLLOWING AKI (N=2451 +AKI/41,160 -AKI)

Chi-yuan Hsu et al. JASN doi:10.1681/ASN.2014111114

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Adjusted OR for HTN:

1.40 (1.28-1.54)

1.36 (1.25-1.49)

1.27 (1.17-1.39)

1.22 (1.12-1.33)

Adjusted for age at index hospitalization, sex, race, body mass index, last ambulatory systolic and diastolic BP measurements, smoking status, diabetes mellitus, chronic heart failure, coronary heart disease, last ambulatory eGFR, and proteinuria.
1 in 5 Patients with AKI Are Re-Hospitalized Within 30 Days (N=111,778 Matched Pairs)

HR 1.53 [95% CI: 1.50-1.57]

18% Rehospitalized
10% ER Visit
Est. cost of readmission = $40 million/yr

CKD Progression is Often NOT Linear
(N=846)
AKI Survivors are at High Risk For Recurrent AKI (N=11,683)

49% Rehospitalized at least once
25% With at least one episode of recurrent AKI
23% Died

Median Time to Recurrent AKI
64 (IQR:19-167) days
Risk Factors for Recurrent AKI Are Not Limited to Age and CKD

1 in 5 AKI Survivors Regularly Use NSAIDs in the Southern Community Cohort Study (N=826)
Awareness of AKI or Having a Problem with Kidney Health Among Patients with KDIGO Stage II-III AKI (N=137)

- **Aware AKI**
  - Yes: 20%
  - No: 80%

- **Yes AKI; Yes problem**
  - 15%

- **No AKI; Yes problem**
  - 27%

- **Yes AKI; No problem**
  - 5%

- **No AKI; No problem**
  - 53%

Knowledge of AKI Risk Factors Among Patients with AKI Stage II-III
Is Recurrent AKI Preventable?

- Nephrotoxin Avoidance
- Volume Management?
- Optimal BP?
- RAAS Inhibition?
## RAAS Inhibition post-AKI?

<table>
<thead>
<tr>
<th>Event</th>
<th>#Events/#Patients</th>
<th>Crude HR</th>
<th>Adjusted HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause Mortality</td>
<td>3713/9456 (39%)</td>
<td>0.89 (0.85-0.93)</td>
<td>0.85 (0.81-0.89)</td>
</tr>
<tr>
<td>Hospitalization for a renal cause</td>
<td>549/9414 (6%)</td>
<td>1.31 (1.15-1.49)</td>
<td>1.28 (1.12-1.46)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>407/9427 (4%)</td>
<td>1.26 (1.09-1.46)</td>
<td>1.25 (1.08-1.46)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>73/9455 (&lt;1%)</td>
<td>1.47 (1.08-2.29)</td>
<td>1.56 (1.07-2.27)</td>
</tr>
</tbody>
</table>

Other Outcomes of Interest?
Adverse Drug Events in Older U.S. Adults Tend to Involve Drugs Cleared by the Kidney

- 25% Insulin or oral hypoglycemics
- 11% Opioids
- 8% Antibiotics/Digoxin
- ? Thrombin/Xa Inhibitors

Risk of Hypoglycemia Among AKI Survivors with Diabetes (N=65K matched pairs)

Events per 100 PYs
30 (29-30)
24 (23-24)

adjusted HR 1.26, 95% CI: 1.21-1.32

Hung, AM, et al. Diabetes Care 2018; 41(3) 503-12
Poor Recovery Increases Risk for Hypoglycemia After AKI Among Patients with Diabetes

Hung, AM, et al. Diabetes Care 2018; 41(3) 503-12
Health Utilities Index Scores are Low Among 60-day Survivors of the ATN Study (N=414)

Mean Age 58±15
Mean Score 0.4±0.37
Mean Population Score for Aged 75-89 = 0.75
Mean Score for Incident (3 mo) dialysis = 0.73

Johansen K L et al. CJASN 2010;5:1366-1372
Reasons to Address Long-Term Goals Following Hospitalization

- Risk of rehospitalization/death are high
- It will be an informed discussion
- Good opportunity to coordinate with PCP
- Other home caregivers more likely to be available and engaged
- Optimal time to listen for patient preferences and to engage in shared-decision making
Probability of Developing Frailty Increases with AKI Stage in Critically Ill
(No AKI N=74, AKI N=243)

Abdel-Kader, K et al. *Crit Care Med* 2018; 46(5):e380-88
Transition to Chronic Dialysis– House Maintenance

**PICC Line Use increasing**
- 942,000 sold in US/annually

Sadfar N, Chest 2005; 128(2):489-95
Medtech Insight

**Case Control Study, N=282 w/o nonrecovered AKI**
- 120 non-AVF(catheter/AVG) vs. 162 AVF
- % PICC: 44.2% non-AVF vs. 19.7% in AVF, p< 0.001
- Adjusted OR for non-AVF 2.5 (1.2-5.4)
  Gender, vein/artery size, and any CVC

Ters, ME AJKD 2012; 60(4):601-608
Summary

• The number of AKI survivors is growing
• Survivors are at risk for future loss of kidney function, cardiovascular disease, death, and disability/poor QoL
• Proportion who follow-up with Nephrology is low

....BUT, Optimal Care Strategies Need to be Defined
Potential Domains to Improve Post-AKI Care

- Monitoring for recovery/recurrent AKI

- Identification and Referral for those at High Risk (duration, severity, ? Biomarkers/RFR)

- Recognition/Treatment of intermediate targets (proteinuria, BP)

- Prevention of Recurrent AKI/rehospitalizations (nephrotoxin use, ? blood pressure/volume/RAAS?), Adverse Drug Events

- Critical Patient-Centered targets: HrQOL/Frailty, symptom management, educational awareness, transitions to ESRD or conservative care, nutrition
Acknowledgements

- Funding
- VA HSR&D IIR 13-073
- ASSESS-AKI (DK92192-07)
- Vanderbilt Center for Kidney Disease (VCKD)