The KDIGO AKI Guidelines: from 2011-2019

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Guangzhou, November 22, 2019
Topics of 2012 AKI guidelines and recommendations

- Section 2: AKI Definition, Staging and Risk Assessment
- Section 3: Prevention and Treatment of AKI
- Section 4: Contrast-induced AKI
- Section 5: Dialysis Interventions for Treatment of AKI

87 recommendations
22 of level 1: “we recommend”
39 of level 2: “we suggest”
KDIGO definition and classification of AKI

**Diagnostic criteria for AKI:**
- Serum-creatinine increase $\geq 0.3$ mg/dl within 48h **OR**
- Serum-creatinine increase $\geq 1.5$ times baseline, which is known or presumed to have occurred within the last 7 days **OR**
- Urine volume $< 0.5$ ml/kg for 6 h

**Scoring System:**

- Stage 1:
  - SCr $\geq 0.3$ mg/dl OR
  - Increase to 1.5-1.9 times from baseline
- Stage 2:
  - SCr increase to $\geq 3$ times from baseline
  - OR
  - SCr $\geq 4.0$ mg/dl OR
  - RRT
- Stage 3:
  - UO $< 0.5$ ml/kg/h for 6-12 h
  - OR
  - UO $< 0.5$ ml/kg/h for $\geq 12$ h
  - OR
  - UO $< 0.3$ ml/kg/h for $\geq 24$ h OR anuria for $\geq 12$ h
Limitations of the KDIGO definitions and staging of AKI

• Many etiologies cause AKI
  • Criteria do not distinguish between the multiple etiologies that cause AKI
  • Should management be individualized on a better phenotyping of AKI by etiology, severity of injury, and ability to recover?

• Use of urine output as a sole criterium of AKI

• Problems with SCr kinetics reflecting GFR

• Determination of baseline serum creatinine
  • Should the first documented SCr at hospitalization be used as the baseline, rather than using historical values?
  • relying on small changes in SCr for the diagnosis of AKI may be associated with a high rate of misdiagnosis, especially in patients with a baseline SCr ≥1.5 mg/dL
Time to reach AKI diagnosis by sCr and UO criteria in non-oliguric, and oliguric AKI with sCr and without sCr change oliguric patients

Clinical ICU outcomes by AKI diagnosis criteria

Acute elevations of serum creatinine: Implications are context-dependent

**Good**
- "Induced AKI"
  - Diuresis/Decongestion in HF
  - RAAS Inhibition
  - Intensive BP Control
  - SGLT2i

**Outcomes Better**

**Bad**
- "Spontaneous AKI"
  - Untreated Cardiorenal s.
  - Hepatorenal s.
  - Sepsis-Induced
  - Nephrotoxin-Induced

**Outcomes Worse**

Coca S. Nephrology Self-Assessment Program - Vol 18, 49-53, 2019
HR of in-hospital death among patients at different stages of AKI in
A: preexisting CKD
B: ICU vs non ICU
C: duration of AKI

“Transient”: AKI recovery within 3 days


**Incidence of AKI in various clinical settings**
9 medical centers South China

Overall incidence AKI 11.6%
CA: 2.5%
HA: 9.1%
Potential SCr trajectories and AKI misclassification

The conceptual overlap among AKI, AKD and CKD (KDIGO AKI guideline 2012)

ADQI model
### Criteria for KDIGO Definitions of Kidney Diseases and Disorders

<table>
<thead>
<tr>
<th>Criteria</th>
<th>AKI</th>
<th>AKD</th>
<th>CKD</th>
<th>NKD*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration</strong></td>
<td>Within 7 days</td>
<td>≤3 months</td>
<td>&gt;3 months</td>
<td></td>
</tr>
<tr>
<td><strong>Function Alteration</strong></td>
<td>Oliguria for ≥6 hours, or</td>
<td>AKI, or GFR &lt;60 ml/min/1.73 m², or</td>
<td>GFR &lt;60 ml/min/1.73 m², or</td>
<td>GFR ≥60 ml/min/1.73 m², and Stable Scr</td>
</tr>
<tr>
<td></td>
<td>Increase in Scr by ≥0.3 mg/dl in 48 hours, or</td>
<td>Decrease in GFR by ≥35%, OR Increase in Scr by ≥50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increase in Scr by &gt;50% in 7 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Structural Alteration</strong></td>
<td>Not defined</td>
<td>Marker of kidney damage (albuminuria)</td>
<td>Marker of kidney damage (albuminuria)</td>
<td>No marker of kidney damage</td>
</tr>
</tbody>
</table>

James et al, JAMA Netw Open. 2019 Apr 5;2(4):e191795
### Incidence and Hazard ratio’s for mortality of kidney diseases in Alberta residents, Canada

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Events, No. (%)</th>
<th>Total Follow-up, y</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Crude</td>
</tr>
<tr>
<td>Mortality (n = 1,109,099)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AKD without AKI</td>
<td>67,655 (7.3)</td>
<td>70,2914</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>CKD with AKD without AKI</td>
<td>2,977 (47.2)</td>
<td>37,000</td>
<td>8.33 (8.03-8.65)</td>
</tr>
<tr>
<td>CKD with AKI</td>
<td>3,585 (71.5)</td>
<td>19,574</td>
<td>18.75 (18.13-19.39)</td>
</tr>
<tr>
<td>AKD without AKI</td>
<td>10,940 (25.8)</td>
<td>291,157</td>
<td>3.90 (3.62-3.98)</td>
</tr>
<tr>
<td>AKI</td>
<td>7,964 (50.5)</td>
<td>80,864</td>
<td>10.15 (9.91-10.39)</td>
</tr>
<tr>
<td>CKD</td>
<td>34,816 (29.4)</td>
<td>80,4081</td>
<td>4.50 (4.44-4.55)</td>
</tr>
</tbody>
</table>

#### Incidence

- **AKD without AKI**: 3.8/100 adults tested
- **AKI**: 1.4/100 adults tested
- **CKD**: 10.6/100 adults tested

James et al, JAMA Netw Open. **2019** Apr 5;2(4):e1
New Tools for Risk Assessment

RISK ASSESSMENT TOOLS SINCE 2012:
- RENAL ANGINA INDEX
- RENAL FUNCTIONAL RESERVE ASSESSMENT
- NEW BIOMARKERS
  - NGAL, (lipocalin-2)
  - G1- Cell cycle arrest proteins (TIMP-2*IGFBP7)

Neutrophil gelatinase-associated lipocalin
Tissue inhibitor of metalloproteinases-2- insulin-like growth factor binding protein 7
Idealized GFR vs SCr showing renal reserve in a patient with normal kidney function

For SCr to rise 67% of total functions must be lost

Preoperative Renal Functional Reserve Predicts Risk of AKI Post Cardiac Surgery

Patients with preoperative RFR ≤15ml/min/1.73m² were 11.8 times more likely to develop AKI.

Roles of novel biomarkers

1. Diagnosis
   - Detection of early injury
   - Location and etiology
   - Determination of therapy

2. Early Prognosis
   - Extent of injury?
   - Ongoing injury?
   - Initiation of recovery?
   - Risk of worsening?

3. Later Course
   - Risk of future CKD/ESRD?
   - Risk of mortality?
   - Renal reserve?

AKI Insult

Serum Creatinine

ESRD Results

CKD Results

Full Recovery
Cell cycle inhibitor marker (TIMP-2)x(IGFBP7) levels are associated with adverse outcomes in ICU with AKI

Subclinical AKI?

Hemodynamic Prerenal AKI?

Xie Y et al, Kidney Int (2019) 95, 1486–1493
Urinary Matrix Metalloproteinase-7 Predicts Severe AKI and Poor Outcomes after Cardiac Surgery

uMMP-7 level peaked within 6 hours after surgery (A) and quintiles of uMMP-7 levels within the first 6 hours had a graded relationship with the incidence of severe AKI (B).

Urinary matrix metalloproteinase-7 (uMMP-7) levels reflect the activity of intrarenal Wnt/b-catenin

Xiaobing Yang et al. JASN 2017;28:3373-3382
Preventive strategy performed in high risk on pump cardiac surgery patients-single center trial

Application of the “KDIGO care bundle” reduced overall AKI at 72 h from 71% to 55.1% and the rates of moderate-to-severe AKI from 44.9% to 29.7%.

Meersch et al, Int Care Med 2017, 43:1551–1561
Limitations of SCr-based AKI definition

Moledina, Parikh, Semin Nephrol 38:3-11, 2017
Conclusions

• Targeting a mean arterial pressure of 80 to 85 mm Hg, as compared with 65 to 70 mm Hg, in patients with septic shock undergoing resuscitation did not result in significant differences in mortality at either 28 or 90 days.

• Sub group analysis: in patients with chronic hypertension (n:340) significantly less RRT in high pressure target group (31.7 vs 42.2%) p =0.046; but no direct relationship between AKI and mortality.
Type of Vasopressor

It is not known which vasopressor agent is most effective for prevention or treatment of patients with AKI and septic shock. Most studies have focused on norepinephrine, dopamine, or vasopressin.

Angiotensin II for Vasodilatory Shock, resistant to high doses of vasopressors-ATHOS-3

**Table 2. Primary and Secondary End Points.**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Angiotensin II (N=163)</th>
<th>Placebo (N=158)</th>
<th>Odds or Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy end point: MAP response at hour 3 — no. (%)†</td>
<td>114 (69.9)</td>
<td>37 (23.4)</td>
<td>Odds ratio, 7.95 (4.76–13.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary efficacy end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in cardiovascular SOFA score at hour 48‡</td>
<td>−1.75±1.77</td>
<td>−1.28±1.65</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Mean change in total SOFA score at hour 48§</td>
<td>1.05±5.50</td>
<td>1.04±5.34</td>
<td></td>
<td>0.49</td>
</tr>
<tr>
<td>Additional end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in norepinephrine-equivalent dose from baseline to hour 3¶</td>
<td>−0.03±0.10</td>
<td>0.03±0.23</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All-cause mortality at day 7 — no. (%)</td>
<td>47 (29)</td>
<td>55 (35)</td>
<td>Hazard ratio, 0.78 (0.53–1.16)</td>
<td>0.22</td>
</tr>
<tr>
<td>All-cause mortality at day 28 — no. (%)</td>
<td>75 (46)</td>
<td>85 (54)</td>
<td>Hazard ratio, 0.78 (0.57–1.07)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Fluid Therapy: Unanswered Questions

When should fluids be given?
How should they be given?
What are the therapeutic targets?
How should fluid therapy be monitored?
What are the indications for fluid removal?
How should fluid removal be monitored?
# Role of Hemodynamic Optimisation

A Randomized Trial of Protocol-Based Care for Early Septic Shock- The ProCESS Investigators-The Univ of Pittsburg

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Protocol-based EGDT (N = 439)</th>
<th>Protocol-based Standard Therapy (N = 446)</th>
<th>Usual Care (N = 456)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-hospital death by 60 days: primary outcome</td>
<td>92/439 (21.0)</td>
<td>81/446 (18.2)</td>
<td>86/456 (18.9)</td>
<td>0.83‡</td>
</tr>
<tr>
<td>Death by 90 days</td>
<td>129/405 (31.9)</td>
<td>128/415 (30.8)</td>
<td>139/412 (33.7)</td>
<td>0.66</td>
</tr>
<tr>
<td>New organ failure in the first week — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>269/439 (61.3)</td>
<td>284/446 (63.7)</td>
<td>256/456 (56.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Respiratory</td>
<td>165/434 (38.0)</td>
<td>161/441 (36.5)</td>
<td>146/451 (32.4)</td>
<td>0.19</td>
</tr>
<tr>
<td>Renal</td>
<td>12/382 (3.1)</td>
<td>24/399 (6.0)</td>
<td>11/397 (2.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Duration of organ support — days§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>2.6±1.6</td>
<td>2.4±1.5</td>
<td>2.5±1.6</td>
<td>0.52</td>
</tr>
<tr>
<td>Respiratory</td>
<td>6.4±8.4</td>
<td>7.7±10.4</td>
<td>6.9±8.2</td>
<td>0.41</td>
</tr>
<tr>
<td>Renal</td>
<td>7.1±10.8</td>
<td>8.5±12</td>
<td>8.8±13.7</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Restricting resuscitation fluid in septic shock (CLASSIC trial)

Restrictive (n:1490) vs liberal fluid (n:1493) administration during major abdominal surgery


Restrictive: total 24 h peri and post op: 3.7 liters (IQR: 2.9 to 4.9)
Liberal: total 24 h peri and post op: 6.1 liters (IQR: 5.0 -7.4)

AKI restrictive: 8.6%
AKI liberal: 5.0% (p<0.001)
The effects of IV fluids on the plasma properties

Effects of balanced crystalloids compared to saline on in-hospital mortality in ICU patients

Secondary Analysis of SMART Trial in sepsis
30 d mortality significantly lower in Balanced group
Brown et al, AJRCCM (August, 2019)

Semler, Kellum Am J Respir Crit Care Med 15;199(8):952-960, 2019
3.8.1: We suggest not using aminoglycosides for the treatment of infections unless no suitable, less nephrotoxic, therapeutic alternatives are available. (2A)

3.8.2: We suggest that, in patients with normal kidney function in steady state, aminoglycosides are administered as a single dose daily rather than multiple-dose daily treatment regimens. (2B)

3.8.6: We suggest using lipid formulations of amphotericin B rather than conventional formulations of amphotericin B. (2A)

4.4.1: We recommend iv volume expansion with either isotonic sodium chloride or sodium bicarbonate solutions rather than no iv volume, in patients at increased risk for CI-AKI. (1A)

4.4.3: We suggest using oral NAC with iv isotonic crystalloids in patients at increased risk of CI-AKI. (2D)
Controversies: contrast associated AKI in high risk patients (CKD, proteinuria, diabetes)

The NEW ENGLAND JOURNAL of MEDICINE

Outcomes after Angiography with Sodium Bicarbonate and Acetylcysteine


CONCLUSIONS

there was no benefit of intravenous sodium bicarbonate over intravenous sodium chloride or of oral acetylcysteine over placebo for the prevention of death, need for dialysis, or persistent decline in kidney function at 90 days or for the prevention of contrast-associated acute kidney injury.
Differences in design and outcomes between the ELAIN and AKIKI trials

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ELAIN trial</th>
<th>AKIKI trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td>Germany</td>
<td>France</td>
</tr>
<tr>
<td>Number of Sites</td>
<td>1</td>
<td>31</td>
</tr>
<tr>
<td>Number of participants</td>
<td>231</td>
<td>620</td>
</tr>
<tr>
<td>ARR for sample size calculation</td>
<td>18%</td>
<td>15%</td>
</tr>
<tr>
<td>Criteria for early intervention strategy</td>
<td>KDIGO stage 2</td>
<td>KDIGO stage 3</td>
</tr>
<tr>
<td>Criteria for delayed intervention strategy</td>
<td>KDIGO stage 3</td>
<td>Specific criteria*</td>
</tr>
<tr>
<td>Mean SOFA score of enrolled patients</td>
<td>~16.0</td>
<td>~10.9</td>
</tr>
<tr>
<td>Primary end point</td>
<td>90 day mortality</td>
<td>60 day mortality</td>
</tr>
<tr>
<td>End point mortality – early intervention strategy</td>
<td>39.3%</td>
<td>48.5%</td>
</tr>
<tr>
<td>End point mortality – delayed intervention strategy</td>
<td>54.7%</td>
<td>49.7%</td>
</tr>
<tr>
<td>Proportion of patients in the delayed intervention group who received RRT</td>
<td>90.8%</td>
<td>51.0%</td>
</tr>
</tbody>
</table>

ARR, absolute risk reduction in primary end point; KDIGO, Kidney Disease: Improving Global Outcomes
RRT, renal replacement therapy; SOFA, sepsis-related organ failure assessment. *Oliguria or anuria for >72 h, serum urea >40 mmol/l, serum potassium >6 mmol/l (or >5.5 mmol/l despite medical intervention), blood pH <7.15, or acute pulmonary oedema causing significant hypoxaemia.

Timing of RRT in patients with AKI and sepsis

Early start: within 12 h after diagnosis AKI
N: 246

Delayed start: after 48 h after diagnosis AKI
N: 242

Pts receiving RRT

62 % + 17%
97%

Definitions and epidemiology of early or late reversal and functional recovery of AKI in ICU

Recovery: reversibility at hospital discharge

AKI stage 2/3

Source Population

45,568

Study Cohort*

16,968

Early Reversal

10,830

(63.8%)

No Early Reversal

6,138

(36.2%)

Early Reversal

4,508

(26.6%)

4,496

(26.5%)

1,642

(9.7%)

Late Reversal

Sustained Reversal

Relapse Recovery

Relapse No Recovery

5 profiles

Reversal: return to non AKI stage

Days 0-7

Days 8+

9,976 (58.8%) Recovered at Hospital Discharge

Kellum et al, Am J Respir Crit Care Med 195, 784–791, 2017
Different types of recovery after AKI-survival to death or RRT

Kellum et al, Am J Respir Crit Care Med 195, 784–791, 2017
Association of AKI with 30-day hospital readmission in a propensity-matched cohort—most responsible diagnosis during index hospitalization

Cumulative mortality by acute kidney injury (AKI) stage (1-3 denote severity stage), stratified by baseline kidney function

Cumulative incidences of subsequent renal progression (solid line) for those with (red) and without (blue) an AKI admission in 2003, grouped by 1 year post-episode eGFR and accounting for the competing risk of death (dashed line) – Grampian study population

What the 2012 AKI KDIGO guideline has accomplished
