Perioperative Management of Acute Kidney Injury

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Objectives: Discuss best practices and appropriate management to prevent and treat perioperative acute kidney injury

Disclosures: None

Acknowledgments: MUSC, NIGMS
What is Perioperative Acute Kidney Injury?
How is AKI defined?

Dialysis?
AKI defined?
2.1.1: AKI is defined as any of the following (Not Graded):
- Increase in SCr by $\geq 0.3$ mg/dl ($\geq 26.5$ μmol/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 $< 0.5$ ml/kg/h for 6 hours.

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

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Staging of AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td>1</td>
<td>1.5–1.9 times baseline OR $\geq 0.3$ mg/dl ($\geq 26.5$ μmol/l) increase</td>
</tr>
<tr>
<td>2</td>
<td>2.0–2.9 times baseline</td>
</tr>
<tr>
<td>3</td>
<td>3.0 times baseline OR Increase in serum creatinine to $\geq 4.0$ mg/dl ($\geq 353.6$ μmol/l) OR Initiation of renal replacement therapy OR In patients $&lt; 18$ years, decrease in eGFR to $&lt; 35$ ml/min per 1.73 m²</td>
</tr>
</tbody>
</table>

Why is AKI important?
The incidence of AKI is increasing.

Hsu C-y *Kidney International*. 2003

Number per 100,000 person years

- 1996-1997: 322.7
- 1998-1999: 388.3
- 2000-2001: 453.6
- 2002-2003: 522.4
AKI independently predicts death.
AKI independently predicts CKD.

AKI independently predicts death.

Heart
- ↑ IL-1, IL-6, TNF-α
- Neutrophil infiltration
- ↓ LV Fractional shortening
- Myocyte apoptosis

Brain
- ↑ GFAP
- ↑ Vascular permeability
- Encephalopathy

Lungs
- ↑ Vascular permeability
- Na⁺ channels downregulated
- Pulmonary edema
- Alveolar hemorrhage
- Endothelial cell apoptosis

Liver
- ↑ ICAM-1, IL-6, TNF-α
- Transaminitis
- Neutrophil infiltration
- Oxidative stress
- Periportal necrosis

Intestines
- ↑ IL-17A
- ↑ Vascular permeability
- Neutrophil infiltration
- Villous endothelial cell apoptosis
- Villous epithelial cell necrosis
Why does surgery cause AKI?

1. Tissue trauma

2. Hemodynamic instability
1. Tissue trauma
2. Hemodynamic instability
2. Hemodynamic instability

2. Hemodynamic instability
2. Hemodynamic instability
*Adjusted for age, gender, race, diabetes, ACE-inhibitor or aldosterone antagonist use, baseline creatinine, valvular heart surgery, use and duration of cardiopulmonary bypass.

50% increases in $F_2$-isoprostanes $= 38.1\%$ increase in odds of AKI*

Nephron Repair or Deterioration

<table>
<thead>
<tr>
<th>Repair and recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adaptive repair</strong>&lt;br&gt;(can result in recovery)</td>
</tr>
<tr>
<td><strong>Maladaptive repair</strong>&lt;br&gt;(can develop into chronic kidney disease)</td>
</tr>
</tbody>
</table>

**Brush border**

- Angiogenesis
- Appropriate inflammation
- Epigenetic changes
- Heme oxygenase 1
- Limited TGF-β expression
- Macrophage subsets
  - T-cell subsets
    - Tregs
    - BMP-7
    - Interleukin-10
    - Interferon-γ

**Necrosis and apoptosis**

**Cell-cycle effects**

**Thinned basement membrane**

- Vascular dropout
- Tubular dropout
- Fibrosis
- Epigenetic changes
- Premature cell-cycle arrest
- Persistent inflammation
- Nephrotoxins
- Repetitive injury
- Unopposed TGF-β
- Macrophage subsets
  - T-cell subsets
  - Interleukin-13

Chawla et al, *NEJM*, 2014
Why does surgery cause AKI?

1. Tissue trauma

2. Hemodynamic instability
AKI Risk Factors

- Chronic kidney disease
- Age
- Diabetes
- COPD
- Liver disease with ascites
- Hypertension
- Gender
- Body Mass Index
- Congestive heart failure
- Decreased LVEF
- Increased central venous pressure

- Hypotension
- Vasopressors
- Anemia
- Transfusion
- Plasma free Hb
- Myoglobin
- Aminoglycosides
- NSAIDS
- Diuretics
- Cyclosporin & Tacrolimus
- Amphotericin
Modifiable Risk Factors

- Chronic kidney disease
- Age
- Diabetes
- COPD
- Liver disease with ascites
- Hypertension
- Gender
- Body Mass Index
- Congestive heart failure
- Decreased LVEF
- Increased central venous pressure
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- Amphotericin
Why does surgery cause AKI?

1. Tissue trauma

2. Hemodynamic instability
Steroids do not decrease AKI.

<table>
<thead>
<tr>
<th>No. (%) of Patients</th>
<th>Dexamethasone (n = 2235)</th>
<th>Placebo (n = 2247)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary study end point&lt;sup&gt;a&lt;/sup&gt;</td>
<td>157 (7.0)</td>
<td>191 (8.5)</td>
<td>0.83 (0.67-1.01)</td>
</tr>
<tr>
<td>Components of the primary study end point</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>31 (1.4)</td>
<td>34 (1.5)</td>
<td>0.92 (0.57-1.49)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>35 (1.6)</td>
<td>39 (1.7)</td>
<td>0.90 (0.57-1.42)</td>
</tr>
<tr>
<td>Stroke</td>
<td>29 (1.3)</td>
<td>32 (1.4)</td>
<td>0.91 (0.55-1.50)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>28 (1.3)</td>
<td>40 (1.8)</td>
<td>0.70 (0.44-1.14)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>67 (3.0)</td>
<td>97 (4.3)</td>
<td>0.69 (0.51-0.94)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Primary study end point was a composite of death, myocardial infarction, stroke, renal failure, or respiratory failure, within 30 days after surgery.
Perioperative ACE-inhibitors, aldosterone antagonists, and AKI

Statins
Nephrotoxins increase risk for AKI

Bell et al, JASN. 2014.
What is Perfusion?

\[ CO = \frac{(MAP - CVP) \times 80}{SVR} \]

\[ MAP = \frac{(SVR \times CO) + CVP}{80} \]
Fenoldopam Increases Renal Blood Flow

Dopamine does not decrease creatinine rise

### Perioperative Hemodynamic Optimization and AKI

<table>
<thead>
<tr>
<th>Studies</th>
<th>Treatment Events</th>
<th>Treatment Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bender</td>
<td>0</td>
<td>51</td>
<td>0</td>
<td>53</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Berlauk</td>
<td>1</td>
<td>68</td>
<td>1</td>
<td>21</td>
<td>0.30 [0.02, 4.99]</td>
</tr>
<tr>
<td>Bishop</td>
<td>6</td>
<td>50</td>
<td>16</td>
<td>65</td>
<td>0.42 [0.15, 1.16]</td>
</tr>
<tr>
<td>Bonazzi</td>
<td>0</td>
<td>50</td>
<td>0</td>
<td>50</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Boyd</td>
<td>3</td>
<td>53</td>
<td>7</td>
<td>54</td>
<td>0.40 [0.10, 1.65]</td>
</tr>
<tr>
<td>Chytra</td>
<td>0</td>
<td>80</td>
<td>1</td>
<td>82</td>
<td>0.34 [0.01, 8.41]</td>
</tr>
<tr>
<td>Donati</td>
<td>2</td>
<td>68</td>
<td>7</td>
<td>67</td>
<td>0.26 [0.05, 1.30]</td>
</tr>
<tr>
<td>Gan</td>
<td>2</td>
<td>50</td>
<td>4</td>
<td>50</td>
<td>0.48 [0.08, 2.74]</td>
</tr>
<tr>
<td>Lobo</td>
<td>2</td>
<td>19</td>
<td>1</td>
<td>18</td>
<td>2.00 [0.17, 24.19]</td>
</tr>
<tr>
<td>Malhotra</td>
<td>1</td>
<td>13</td>
<td>1</td>
<td>14</td>
<td>1.08 [0.06, 19.31]</td>
</tr>
<tr>
<td>McKendry</td>
<td>1</td>
<td>89</td>
<td>3</td>
<td>85</td>
<td>0.31 [0.03, 3.05]</td>
</tr>
<tr>
<td>Noblett</td>
<td>0</td>
<td>51</td>
<td>2</td>
<td>52</td>
<td>0.20 [0.01, 4.19]</td>
</tr>
<tr>
<td>Pearse</td>
<td>3</td>
<td>62</td>
<td>4</td>
<td>60</td>
<td>0.71 [0.15, 3.32]</td>
</tr>
<tr>
<td>Polonen</td>
<td>1</td>
<td>196</td>
<td>3</td>
<td>197</td>
<td>0.33 [0.03, 3.22]</td>
</tr>
<tr>
<td>Sandham</td>
<td>70</td>
<td>941</td>
<td>95</td>
<td>965</td>
<td>0.74 [0.53, 1.02]</td>
</tr>
<tr>
<td>Shoemaker</td>
<td>0</td>
<td>28</td>
<td>14</td>
<td>60</td>
<td>0.06 [0.00, 0.98]</td>
</tr>
<tr>
<td>Valentine</td>
<td>4</td>
<td>60</td>
<td>1</td>
<td>60</td>
<td>4.21 [0.46, 38.86]</td>
</tr>
<tr>
<td>Wakeling</td>
<td>3</td>
<td>64</td>
<td>2</td>
<td>64</td>
<td>1.52 [0.25, 9.45]</td>
</tr>
<tr>
<td>Wilson</td>
<td>16</td>
<td>92</td>
<td>13</td>
<td>46</td>
<td>0.53 [0.23, 1.24]</td>
</tr>
<tr>
<td>Ziegler</td>
<td>0</td>
<td>32</td>
<td>0</td>
<td>40</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

Total events (95% CI) 2117 / 2103 0.64 [0.50, 0.83]

Total events 115 / 175

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 12.45$, df = 16 (P = 0.71); $I^2 = 0%$

Test for overall effect: $Z = 3.37$ (P = 0.0007)

Hydroxyethyl starches increase risk for RRT

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Events HES</th>
<th>Total HES</th>
<th>No. of Events Control</th>
<th>Total Control</th>
<th>RR (95% CI)</th>
<th>Favor HES</th>
<th>Favors Control</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berard et al, 1995</td>
<td>5</td>
<td>155</td>
<td>4</td>
<td>152</td>
<td>1.23 (0.34-4.48)</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Schortgen et al, 2001</td>
<td>13</td>
<td>65</td>
<td>11</td>
<td>64</td>
<td>1.16 (0.56-2.40)</td>
<td>3.3</td>
<td></td>
<td>3.3</td>
</tr>
<tr>
<td>Brunkhorst et al, 2008</td>
<td>81</td>
<td>297</td>
<td>51</td>
<td>303</td>
<td>1.62 (1.19-2.21)</td>
<td>18.0</td>
<td></td>
<td>18.0</td>
</tr>
<tr>
<td>McIntyre et al, 2008</td>
<td>3</td>
<td>21</td>
<td>1</td>
<td>19</td>
<td>2.71 (0.31-23.93)</td>
<td>0.4</td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>Du et al, 2011</td>
<td>1</td>
<td>21</td>
<td>0</td>
<td>21</td>
<td>3.00 (0.13-69.70)</td>
<td>0.2</td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>James et al, 2011</td>
<td>2</td>
<td>58</td>
<td>3</td>
<td>57</td>
<td>0.66 (0.11-3.78)</td>
<td>0.6</td>
<td></td>
<td>0.6</td>
</tr>
<tr>
<td>Viachou et al, 2010</td>
<td>0</td>
<td>12</td>
<td>0</td>
<td>17</td>
<td>Not estimable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pernier et al, 2012</td>
<td>87</td>
<td>400</td>
<td>65</td>
<td>400</td>
<td>1.34 (1.00-1.79)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myburgh et al, 2012</td>
<td>235</td>
<td>3500</td>
<td>196</td>
<td>3500</td>
<td>1.20 (1.00-1.44)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guidet et al, 2012</td>
<td>21</td>
<td>100</td>
<td>11</td>
<td>96</td>
<td>1.83 (0.93-3.59)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td><strong>4629</strong></td>
<td></td>
<td><strong>4629</strong></td>
<td></td>
<td><strong>1.32 (1.15-1.50)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 448 (HES) 342 (Control)

Heterogeneity: $I^2 = 0.00; \chi^2 = 5.07; (P = .75); I^2 = 0$

Test for overall effect: $Z = 4.08, (P < .001)$

Sodium bicarbonate infusion does not reduce AKI.

Sodium bicarbonate infusion does not reduce AKI.

Chloride restrictive strategy reduces AKI.

Yunos et al, *JAMA*, 2012
Chloride restrictive strategy reduces RRT.

Yunos et al, JAMA, 2012
Perioperative RBC Transfusions and AKI

Karkouti et al, Circulation, 2009
Plasma free hemoglobin and AKI

P = 0.006
repeated
measures
ANOVA

* P < 0.01 vs. No AKI

Free Hb (milligrams / dl)

AKI
No AKI

Billings et al, FRBM, 2011
Fluid overload at time of AKI diagnosis associated with death.

Elevated CVP Increases AKI Risk

Dose of RRT in critically ill patients does not affect mortality.

Dose of RRT in critically ill patients does not affect mortality.

Recommendations to avoid and treat perioperative AKI

1. Continue statins and ACE-inhibitors in those patients already taking these drugs.
2. Maintain consistent systemic perfusion and blood pressure while avoiding elevated central venous pressures. Make sure cardiac output is maintained in any patient given vasopressors.
3. Give diuretics for hypervolemia and heart failure but not for low urine output.
4. For fluid resuscitation, administer plasmalyte, lactated ringers, or Hartman’s solution. Avoid hyperchloremic fluids including NS and avoid PRBC transfusions. Do not use starch colloid solutions.