Approach to Acute Kidney Injury

Sarah Faubel, MD

What is acute kidney injury (AKI)?

What is AKI?

Acute Dialysis Quality Initiative (ADQI), National Kidney Foundation (NKF), Kidney Disease: Improving Global Outcomes (KDIGO), Acute Kidney Injury Network (AKIN), American Society of Nephrology (ASN), International Society of Nephrology (ISN), European Society of Intensive Care Medicine
What is AKI?

“An abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dL, a percentage increase in serum creatinine of more than or equal to 50% (1.5 fold from baseline), or a reduction in urine output of less than 0.5 mL/kg per hour for more than six hours”


What is AKI?

- A 0.3 mg/dL increase in creatinine is not lab error
- A 0.3 mg/dL increase in serum creatinine is associated with 70% higher OR of death
  - (Chertow, GM, JASN, 2005)
- Nearly 20% of hospitalized develop AKI
  - (Uchino, S, Crit Care Med, 2006)

What is AKI? RIFLE criteria.

- Risk: 1.5x cr (2.5 OR ↑ in hospital mortality)
- Injury: 2.0x cr (5.4 OR ↑ in hospital mortality)
- Failure: 3.0x cr (10.1 OR ↑ in hospital mortality)

Outcome measures
- Loss: complete loss of kidney function needing renal replacement therapy for more than 4 weeks
- Failure: complete failure of kidney function needing renal replacement therapy for more than 3 months
Contrast nephropathy is actually bad for you

I really don’t care if my patient gets AKI (1990s attitude).

- “AKI is bad because people with AKI are already sick”
- “It is the comorbidities that kill people”
- “People die with AKI, not of AKI”
- “AKI is an acceptable and treatable consequence of interventions”

Levy et al. JAMA. 1996;275:1489-1494

The study that challenged the dogma...

- 16,248 patients who received contrast
- 183 subjects developed ARF
  - Increase in serum creatinine of at least 25%
  - Increased creatinine to at least 2 mg/dL
- 174 controls
  - Very well matched patients who did not develop renal failure
- Primary Endpoint: mortality (in hospital)

Levy et al. JAMA. 1996;275:1489-1494
The results that challenged the dogma…

- No AKI -> 7% mortality; With AKI -> 34% mortality
- Adjusted odds ratio of death -> 5.5
- Increased occurrence of the following:
  - Sepsis
  - GI bleeding
  - Delirium
  - Respiratory failure

Levy, E M; JAMA, 1996; PMID: 862223

The conclusions…

“The high mortality rate in AKI is not explained by the underlying conditions alone.”

“AKI appears to increase the risk of developing severe non-renal complications that lead to death and should not be regarded as a treatable complication of serious illness.”

Levy et al JAMA. 1996;275:1489-1494

Corroborating the conclusions: AKI is an independent predictor of mortality

<table>
<thead>
<tr>
<th>ARF characteristics</th>
<th>Adjusted OR of death</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic surgery</td>
<td>9.1</td>
<td>Kashyap, 1997</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>7.9</td>
<td>Chertow, 1998</td>
</tr>
<tr>
<td>Hospital-acquired</td>
<td>2.5</td>
<td>Obialo, 2000</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>6.6</td>
<td>Bates, 2000</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>4.3</td>
<td>Aggarwal, 2001</td>
</tr>
<tr>
<td>Bone marrow transplant</td>
<td>6.8</td>
<td>Parikh, 2005</td>
</tr>
</tbody>
</table>
What is the effect of AKI on mortality in the ICU patient?

<table>
<thead>
<tr>
<th></th>
<th>ICU mortality without AKI</th>
<th>ICU mortality with AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis + AKI</td>
<td>8%</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>14%</td>
<td>43%</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>63%</td>
</tr>
<tr>
<td>Ventilator + AKI</td>
<td>15%</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td>28%</td>
<td>57%</td>
</tr>
<tr>
<td></td>
<td>16%</td>
<td>63%</td>
</tr>
</tbody>
</table>

Schrier et al JCI. 2004; NEJM;351:159-169

Summary: People with AKI are more likely to die

Those who survive have problems too
- Prolonged hospitalization
- Increased mortality after hospital discharge (even 10 years later)
- CKD

Levy, E M; JAMA, 1996; PMID: 862223
Solomon, R; NEJM, 1994; PMID: 7969280
Liss, P; Kidney Int, 2006; PMID: 17003814

OK, OK! AKI is bad!

Assessing risk and preventing contrast nephropathy
Contrast nephropathy

- Characterized by increased creatinine 24 to 72 hrs after IV iodinated radiocontrast administration
- 3rd most common cause of AKI in hospital
- Most typically occurs following
  - cardiac catheterization (50%)
  - contrasted CT scans (30%)
- Although recovery to baseline kidney function is the norm, contrast nephropathy is not benign

Nash, K; AJKJ, 2002; PMID: 11979336

Contrast nephropathy: risk factors

- Chronic kidney disease
- Diabetes
- Dose of contrast

Observed incidence of AKI after percutaneous coronary intervention

<table>
<thead>
<tr>
<th>Creatinine (mg/dL)</th>
<th>All patients</th>
<th>Diabetics</th>
<th>Non-diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 – 1.1</td>
<td>2.4%</td>
<td>3.7%</td>
<td>2.0%</td>
</tr>
<tr>
<td>1.2 – 1.9</td>
<td>2.5%</td>
<td>4.5%</td>
<td>1.9%</td>
</tr>
<tr>
<td>2.0 – 2.9</td>
<td>22.4%</td>
<td>22.4%</td>
<td>22.3%</td>
</tr>
<tr>
<td>3.0 +</td>
<td>30.6%</td>
<td>33.9%</td>
<td>27.4%</td>
</tr>
</tbody>
</table>

Rihal, CS; Circulation, 2002; PMID: 12010907
Risk of developing AKI requiring dialysis after coronary intervention with 250 cc of contrast

<table>
<thead>
<tr>
<th>Calculated creatinine clearance (mL/min)</th>
<th>50</th>
<th>40</th>
<th>30</th>
<th>20</th>
<th>10</th>
</tr>
</thead>
</table>

What is our patient’s kidney function?

McCullough, PA; AmJMed, 1997; PMID: 9375704

Assessing kidney function: MDRD equation (only if creatinine is stable!)

- Glomerular filtration rate (GFR)(mL/min/1.73m²) = 186 x (Pcr)⁻¹.¹⁰⁴ x (age)⁻⁰.²⁰³ x (0.⁷⁴² if female) x (1.²¹⁰ if African American)

http://www.nkdep.nih.gov/professionals/gfr_calculators/idms_con.htm

What is the kidney function? (examples for a 55 y/o white male)

<table>
<thead>
<tr>
<th>Creatinine (mg/dL)</th>
<th>MDRD GFR (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>&gt; 60</td>
</tr>
<tr>
<td>1.5</td>
<td>52</td>
</tr>
<tr>
<td>2.0</td>
<td>37</td>
</tr>
<tr>
<td>2.5</td>
<td>29</td>
</tr>
<tr>
<td>4.5</td>
<td>15</td>
</tr>
<tr>
<td>5.0</td>
<td>13</td>
</tr>
</tbody>
</table>
What is this patient’s stage of kidney disease?

<table>
<thead>
<tr>
<th>Stage of chronic kidney disease (CKD)</th>
<th>GFR (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal kidney function</td>
<td>&gt;90; no proteinuria</td>
</tr>
<tr>
<td>CKD 1</td>
<td>&gt; 90; with proteinuria</td>
</tr>
<tr>
<td>CKD 2</td>
<td>60 to 89</td>
</tr>
<tr>
<td>CKD 3</td>
<td>30 to 59</td>
</tr>
<tr>
<td>CKD 4</td>
<td>15 to 20</td>
</tr>
<tr>
<td>CKD 5</td>
<td>&lt; 15</td>
</tr>
</tbody>
</table>

Risk of developing AKI requiring dialysis after coronary intervention with 250 cc of contrast

<table>
<thead>
<tr>
<th>Calculated creatinine clearance (mL/min)</th>
<th>Creatinine (most likely)</th>
<th>Diabetics</th>
<th>Non-diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>1.5</td>
<td>0.2%</td>
<td>0.04%</td>
</tr>
<tr>
<td>40</td>
<td>2.0</td>
<td>2%</td>
<td>0.3%</td>
</tr>
<tr>
<td>30</td>
<td>2.5</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>20</td>
<td>3.0</td>
<td>43%</td>
<td>12%</td>
</tr>
<tr>
<td>10</td>
<td>5.0</td>
<td>84%</td>
<td>48%</td>
</tr>
</tbody>
</table>

Contrast nephropathy: Prevention 100% effective methods

- Don’t do the study
- Use alternative methods (easier said than done)
  - MRI, but don’t use gadolinium with CKD or AKI!
  - Nephrogenic systemic fibrosis is a horrible disease
  - FDA recommends to avoid gadolinium in
    - ESRD on dialysis
    - GFR < 30 ml/min
    - AKI
- Must get consent if use gadolinium in these settings
- Dialysis after gadolinium may help

McCullough, PA; AmJMed, 1997; PMID: 9375704
Contrast nephropathy: Prevention

- Low or iso-osmolar ionic contrast
- Lowest dose possible of contrast
- Avoid NSAIDs (ACE-I/ARBs ok to continue)
- Hydration
  - Saline (1 mL/kg/hr 6 – 12 hours before and after)
  - Sodium bicarbonate
- Oral N-acetylcysteine (NAC) (not IV)
  - 600 to 1200 mg PO bid, the day before and after
- Dialysis after will not help

Work up of AKI

- Urine studies (on a spot urine)
  - Urine dipstick and urine microscopy
  - Sodium, urea, creatinine, protein, osmolality
  - FeNa = [(Una/Pna)/(Ucr/Pcr)] x 100 (All units mg/dL)
  - FeUrea = [(Uurea/Purea)/(Urea/Purea)] x 100 (mg/dL)
  - Protein/creatinine = 24 hour protein (in grams)
    - e.g. 200 mg/dL/15 mg/dL = 13.3 grams (a lot)
Work-up of AKI

- Think about the odds
  - 70% of hospital-acquired AKI is pre-renal or ATN
  - In the ICU, about _ of AKI is ATN
- Could the patient be obstructed?
  - Check ultrasound if answer is yes

Pre-renal azotemia versus acute tubular necrosis (ATN)

- Pre-renal azotemia is an increase in creatinine and BUN that is due to decreased renal perfusion in which minimal or no structural damage to the kidney has occurred.
- Decreased renal perfusion may be due to
  - 1) intravascular volume depletion (plasma volume)
  - 2) ineffective blood circulation (CO, BP)
  - 3) intra-renal hemodynamic changes

Pre-renal azotemia versus acute tubular necrosis (ATN)

- ATN is decrease in kidney function characterized by an increase in BUN and creatinine due to tubular dysfunction that is commonly caused by
  - Ischemia
  - Nephrotoxins (Contrast, Gent, Ampho)
  - Rhabdomyolysis
  - Sepsis
- ATN is not fluid responsive
Glomerulus

Na⁺ ↔ Na⁺ ↔ Na⁺ ↔ Na⁺ ↔ Na⁺ ↔ Na⁺ ↔ Na⁺ ↔ Na⁺ ↔ Na⁺ ↔ Na⁺

Proximal tubule epithelial cells

Rest of tubule epithelial cells

Ultratrate (tubule lumen)

Urine Na⁺ typically > 40 meq/L

Urine Na⁺ typically <20 meq/L.

Proximal tubule epithelial cells

Rest of tubule epithelial cells

Urine Na⁺

H₂O

urea

Urine osmolality/ spec grav is high

Urine urea is low

Urine Cr is high
Pre-renal azotemia: summary of urine indices

- Urine Na, Fe Na are low (<20; <1%)
- Fe urea is low (less than 35%)
- BUN/serum creatinine is high (>20)
- Urine creatinine/plasma creatinine high (>20)
- Urine osmolality/spec grav is high (>500/1.015)

Acute tubular necrosis: pathophysiology

- Tubular dysfunction
  - Inability to reabsorb sodium
  - Inability to modify urine
  - Thus:
    - urine sodium 40 mEq/L, FeNa >2%, FeUrea >50%
    - Urine osmolality matches serum osmolality
    - (about 300 mOsm); specific gravity of 1.010

- Tubular dysfunction
  - Tubular cells slough off – renal tubular epithelial cells appear in the urine
  - Granular casts appear
### Acute Kidney Injury

- Urine Na < 20
- FeNa < 1%
- FeUrea < 35%
- Ucr/Pcr > 40
- BUN/Pcr > 20
- Urine osmolality > 500
- Specific gravity > 1.010
- Bland

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### Increased creatinine

#### Intrinsic
- Glomerular/vascular
  - Blood, protein, +/RBC casts
- Acute interstitial nephritis
  - Blood, protein, white cells, +/ white blood cell casts
- Acute tubular necrosis
  - Granular casts, tubular epithelial cells
  - Una > 20, FeNa > 2%, FeUrea > 50%
  - Ucr/Pcr < 20, Urine osmolality = 350
  - Specific gravity = 1.010

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### Case: Diagnostic work-up

- FeNa: 4%
- FeUrea: 55%
- Dipstick
  - (-) heme
  - (-) LE
  - (-) nitrate
  - (tr) protein
  - 1.010
What is the cause of the increased creatinine?

- Infectious glomerulonephritis
- Acute tubular necrosis
- Pre-renal azotemia
- Renal atheroemboli
- Acute interstitial nephritis

Pre
- Stand
  - FeNa <1.0%
  - FeUrea <35%

AKI
- Intrinsic
  - Glomerular/vascular
    - Blood, protein, +RBC casts
  - Acute interstitial nephritis
    - Blood, protein, white cells, +/- white blood cell casts
  - Acute tubular necrosis
    - Granular casts
    - FeNa >2%  FeUrea >50%

Post
- Obstruction

Basic Management of AKI (ATN) (including fluids)
Basic management of AKI

- Don’t make things worse
- Avoid nephrotoxins (e.g., IV contrast)
- Adjust medication dosages
  - (true kidney function difficult to determine)
- Avoid meds with no proven benefit
  - (e.g., dopamine, furosemide)

Management of AKI: Dialysis

- Remarkably, even with newer and better dialysis methods, little improvement in AKI mortality
- Method: CRRT and HD both ok
- Three times a week is fine
- Too late is not ok
- BUN 76 mg/dL or greater?

VA/NIH AKI Trial Network, NEJM. 2008;359:7-20

How should IV fluids be managed?

1. Patient should be given 0.9 NS to maintain a mean arterial blood pressure of 65 mmHg
2. Patient should be given 0.9 NS to maintain a urine output of 20 cc/hour
3. 0.9 NS should be avoided
Early, aggressive is good
Fluid management (sepsis)

- Fluid boluses with crystalloid of 500 cc to maintain CVP between 8 and 12
- Vasopressors to maintain MAP of 65 mmHg
- Transfusion to Hct of 30% if ScvO₂ < 70%
- Dobutamine if ScvO₂ still < 70%

<table>
<thead>
<tr>
<th></th>
<th>6 hrs</th>
<th>7 to 72 hrs</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGDT</td>
<td>5</td>
<td>8.6</td>
<td>13.3</td>
</tr>
<tr>
<td>Not EGDT</td>
<td>3.5</td>
<td>10.6</td>
<td>13.4</td>
</tr>
</tbody>
</table>

Conservative is good
Fluid management (without AKI)

- 1000 patients with acute lung injury
- Randomized trial: liberal vs. conservative fluid
- Liberal = +7 Liters/7 days
- Conservative = -100 cc/7 days
- Mortality: same
- Days on mechanical ventilation shorter, no increase in extra-pulmonary organ failures

NHLBI ARDS CTN, NEJM, 2564 – 2575, 2006

Too much, too late is bad
Fluid management (with AKI)

- ATN is not fluid responsive
- Excess fluid does not improve AKI, but increases oxygen requirements
- Positive fluid balance (1L/d vs. 150 cc/d) independently predicted mortality in patients
- Positive fluid balance is a biomarker of poor outcomes in acute kidney injury

Payen, D et al, Critical Care, 12:R74, 2008
In summary

- AKI results in increased morbidity (CKD) and mortality (in-hospital and long term)
- 70% of hospital-acquired AKI is pre-renal azotemia or ATN
- Urine indices are the most useful initial work-up
- Avoid gadolinium in AKI
- Avoid fluid overload in AKI