Acute Kidney Injury

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Acute Kidney Injury

• Prevention strategies
• Prevention of complications
• Treatment: Diuretics and dialysis

Acute kidney injury is a spectrum of disease

Increased serum Cr  Volume overload  Acidosis  Dialysis
Acute Tubular Necrosis is the Most Common Cause of Hospital Acquired AKI

**ACUTE RENAL FAILURE**

- **PRERENAL**
  - Vascular
  - Obstructive
  - Adynamic
  - Acute Tubular Necrosis

- **INTRINSIC RENAL**
  - Ischemic
  - Hypotension
  - Sepsis
  - Prolonged prerenal state
  - Nephrotoxic
  - Aminoglycosides
  - Contrast
  - Myoglobin

- **POSTRERNAL**

**Prevention of AKI**

- Early recognition is key
- Changes in creatinine reflect changes in GFR, which is probably a late manifestation of renal injury
- A "normal" serum creatinine may reflect significant renal insufficiency, in particularly in the elderly

**Prevention of AKI**

- Avoid hypoperfusion
  - Volume depletion
  - Hypotension
Prevention of AKI

- Avoid nephrotoxic medications:
  - NSAIDs
  - Radiocontrast
  - Aminoglycosides
  - Amphotericin
  - ACE inhibitors/Angiotensin receptor blockers
  - Phosphate-based bowel purgatives (Fleets phosphosoda)
  - Colloid volume expanders with increased risk of renal failure: hydroxyethylstarch

Phosphate nephropathy

<table>
<thead>
<tr>
<th>Factor</th>
<th>Early nephrotic</th>
<th>Late nephrotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of onset after bowel preparation</td>
<td>&lt;24h</td>
<td>Days to months</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Lethargy, confusion, seizure, and fainting</td>
<td>Asymptomatic or nonspecific</td>
</tr>
<tr>
<td>Bowel phosphate and calcium levels</td>
<td>Hyperphosphatemia and hypocalcemia</td>
<td>Normal, unless measured within 3 days of bowel preparation</td>
</tr>
<tr>
<td>Phosphate load</td>
<td>Excess</td>
<td>Standard</td>
</tr>
<tr>
<td>Pathology</td>
<td>Unknown</td>
<td>Nephrocalcinosis</td>
</tr>
<tr>
<td>Treatment options</td>
<td>Intravenous fluid, and phosphate binder, intravenous calcium gluconate, and/or hemodiastysis</td>
<td>None</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Recovery, chronic kidney disease, or death</td>
<td>Chronic kidney disease</td>
</tr>
</tbody>
</table>

Lien, Nat Clin Pract Neph 2008

Phosphate nephropathy

- Has been reported in patients with normal/near normal renal function
- Risk factors: elderly, female, hypertension, diabetes, colitis, ACE/ARB, diuretics
Phosphate Nephropathy: Prevention

- Avoid oral sodium phosphate in high risk patients
- Reduce the dose
- Increase the interval between doses
- Administer fluids before prep (minimize volume depletion)
- (Consider checking chemistries on outpatients)

Hetastarch and AKI

- There are now several randomized clinical trials where HES administration has been associated with a higher rate of AKI

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean age (yrs)</th>
<th>n</th>
<th>Serum creatinine</th>
<th>Reduction in ESRD rate (%)</th>
<th>Change in GFR (ml/min/1.73m²)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boyd et al. [1] 2008</td>
<td>64</td>
<td>206</td>
<td>1.4</td>
<td>41</td>
<td>0.4</td>
<td>0.0003</td>
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<tr>
<td>Wheeler [2] 2008</td>
<td>61</td>
<td>134</td>
<td>1.3</td>
<td>45</td>
<td>0.5</td>
<td>0.0003</td>
</tr>
<tr>
<td>Margherio [3] 2008</td>
<td>61</td>
<td>129</td>
<td>1.3</td>
<td>46</td>
<td>0.7</td>
<td>0.0003</td>
</tr>
<tr>
<td>Chalmers [4] 1998</td>
<td>57</td>
<td>194</td>
<td>1.4</td>
<td>46</td>
<td>0.7</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

*HES = hydroxethyl starch; ESRD = end stage renal disease; GFR = glomerular filtration rate

Townsend and Bagshaw, Neph Clin Pract 2008
Prevention of complications

• Nephrogenic systemic fibrosis
  – Associated with use of gadolinium-based MRI contrast agents
  – Has been observed in patients with chronic kidney disease and acute kidney injury
  – Studies to ascertain incidence are ongoing
  – Must weigh risks/benefits of study (and potential risk of contrast nephropathy with alternative imaging modalities)

Prevention of complications

• Perez-Rodriguez, Radiology 2008
  – 33 cases at a single institution, 2003-2008
  – 36.5/100,000 cases 2003-2006
  – 4/100,000 cases 2007-2008
  – All 33 had eGFR < 15mL/min/m2
  – 26 had CKD, 7 had AKI
Prevention of complications

• Prince, Radiology 2008
  – 15 cases at two institutions, 1997-2007
  – 15/8997 (0.17%) patients with high-dose gadolinium administration, no events with standard gadolinium administration
  – All had eGFR < 30mL/min/m²
  – 11 had acute renal failure or acute on chronic renal failure

Prevention of complications

• Nephrogenic systemic fibrosis
  – We do not empirically dialyze patients to remove gadolinium, nor do we perform hemodialysis on PD patients (half life is markedly prolonged with hemodialysis, and is even longer with peritoneal dialysis)
  – For dialysis patients, we do try to dialyze them as soon as possible after the imaging study (so requires some coordination with radiology)

Management of AKI

• Many therapies have been tried:
  – Renal dose dopamine
  – Loop and osmotic diuretics
  – Atrial natriuretic peptide
  – Insulin-like growth factor
  – Fenoldopam
  – Theophylline
  – Calcium channel blockers
Diuretics and AKI

- Rationale: Diuretics may increase urine flow, therefore flushing the renal tubules of casts and shed cells
- Diuretics play an important role in the management of volume overload

Diuretics and AKI

- Cantarovich AJKD 44(2004): 402-9
  - Placebo controlled RCT of furosemide
  - VERY high doses: 25 mg/kg/day of furosemide, up to 2 g/day
  - Eligibility: all subjects had dialysis-requiring acute renal failure
  - No difference in survival (primary endpoint) or renal recovery between treatment groups

Diuretics and AKI

- What can we learn from observational studies?
- Two large observational studies have been published; these are largely contradictory:
Propensity scores:
A way to adjust for differences between patients

Diuretics and AKI
- Observational cohort study of 4 academic medical centers from 1989-1995 (N=552)
- Eligibility: critically ill subjects who had a nephrology consultation during their ICU stay
- Authors used a propensity score based approach to control for differences between those who received diuretics and those who did not
- OR for death in those receiving diuretics: 1.68 (95% CI 1.06-2.64)

Diuretics and AKI
- Uchino et al, CCM 32(2004): 1669-77
- Observational cohort study of 54 ICUs (6 US centers, total N=1754)
- Eligibility: critically ill subjects who met a prespecified definition for AKI
- Again, propensity scores were used to adjust for differences between those treated with diuretics and those who were not
- OR for death in those treated with diuretics: 1.20 (95% CI 0.96-1.5)
Diuretics and AKI

• A RCT is needed to definitively address this question
• If the patient responds to diuretics, would use diuretics to maintain fluid balance/ prevent complications of volume overload….
• However, threshold to control volume with dialysis should be low

Dialysis considerations

• Modality (intermittent versus continuous)
• Timing
• Dose

Department of Veterans Affairs
COOPERATIVE STUDIES PROGRAM

Intensive vs Conventional Renal Support in Acute Renal Failure

Overview of Study Design

Intensive Management Strategy

Conventional Management Strategy

Overview of Study Design

Intermittent Hemodialysis (SOFA Cardiovascular Score 0-2)

CVVHDF or SLED/EDD (SOFA Cardiovascular Score 3-4)

Intensive Management Strategy

Intermittent Hemodialysis 6-times per week (target Kt/V of 1.2/treatment)

CVVHDF with effluent flow of 35 mL/kg/hr or
SLED/EDD 6-times per week (target Kt/V of 1.2/treatment)
Conventional Management Strategy

Intermittent Hemodialysis 3-times per week  
(target Kt/V of 1.2/treatment)

CVVHDF with effluent flow of 20 mL/kg/hr  
or  
SLED/EDD 3-times per week  
(target Kt/V of 1.2/treatment)

Inclusion Criteria

• ARF clinically consistent with a diagnosis of ATN, defined as:
  - clinical setting of acute ischemic or nephrotoxic injury
  - oliguria (< 20 mL/hr) for > 24 hours
  - an increase in $S_{Cr} \geq 2.0$ mg/dL ($\geq 1.5$ mg/dL in females) over a period of $\leq 4$ days

Exclusion Criteria

• Baseline $S_{Cr} > 2$ mg/dL ($1.5$ mg/dL in females)
• ARF believed to be due to an etiology other than ATN
• > 1 hemodialysis treatment or > 24 hours of CRRT
• Kidney transplant
• Weight > 120 kg
• Pregnancy
• Prisoner
• Non-candidacy for RRT
• Not expected to survive 28-days due to underlying medical condition
• CMO status / moribund state
### Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Intensive Management (N=563)</th>
<th>Less-Intensive Management (N=561)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>59.6±16.3</td>
<td>59.7±15.2</td>
<td>0.97</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>72.6</td>
<td>68.6</td>
<td>0.13</td>
</tr>
<tr>
<td>Race/ethnicity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>73.7</td>
<td>75.0</td>
<td>0.43</td>
</tr>
<tr>
<td>Black</td>
<td>16.2</td>
<td>15.7</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>7.8</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2.3</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Primary treating service (%)</td>
<td></td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>Medical</td>
<td>48.3</td>
<td>46.2</td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>40.7</td>
<td>41.8</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>11.0</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>Length of stay pre-randomization Hospital</td>
<td>11.4±13.6</td>
<td>10.7±14.7</td>
<td>0.36</td>
</tr>
<tr>
<td>ICU</td>
<td>6.9±10.1</td>
<td>6.4±7.8</td>
<td>0.38</td>
</tr>
</tbody>
</table>

### Baseline Severity of Illness

<table>
<thead>
<tr>
<th></th>
<th>Intensive Management (N=563)</th>
<th>Less-Intensive Management (N=561)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charlson co-morbidity index</td>
<td>4.7±3.0</td>
<td>4.2±2.8</td>
<td>0.66</td>
</tr>
<tr>
<td>Mechanically ventilated (%)</td>
<td>80.5</td>
<td>80.7</td>
<td>0.91</td>
</tr>
<tr>
<td>Sepsis (%)</td>
<td>83.6</td>
<td>82.4</td>
<td>0.88</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>26.4±7.2</td>
<td>26.1±7.5</td>
<td>0.29</td>
</tr>
<tr>
<td>SOFA score</td>
<td>14.7±3.5</td>
<td>14.4±3.7</td>
<td>0.21</td>
</tr>
<tr>
<td>Respiratory</td>
<td>2.4±1.1</td>
<td>2.3±1.1</td>
<td>0.10</td>
</tr>
<tr>
<td>Coagulation</td>
<td>1.4±1.2</td>
<td>1.3±1.2</td>
<td>0.49</td>
</tr>
<tr>
<td>Liver</td>
<td>1.3±1.3</td>
<td>1.4±1.3</td>
<td>0.29</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>2.3±1.7</td>
<td>2.3±1.7</td>
<td>0.23</td>
</tr>
<tr>
<td>CNS</td>
<td>2.4±1.4</td>
<td>2.5±1.4</td>
<td>0.69</td>
</tr>
<tr>
<td>Cleveland Clinic ICU-ARF score</td>
<td>12.3±3.1</td>
<td>12.0±3.4</td>
<td>0.11</td>
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</table>

### Baseline Renal Function

<table>
<thead>
<tr>
<th></th>
<th>Intensive Management (N=563)</th>
<th>Less-Intensive Management (N=561)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology of AKI (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>82.1</td>
<td>79.7</td>
<td>0.31</td>
</tr>
<tr>
<td>Nephrotoxic</td>
<td>27.8</td>
<td>28.1</td>
<td>0.92</td>
</tr>
<tr>
<td>Sepsis</td>
<td>56.5</td>
<td>33.2</td>
<td>0.29</td>
</tr>
<tr>
<td>Multifactoral</td>
<td>59.4</td>
<td>58.6</td>
<td>0.81</td>
</tr>
<tr>
<td>Oliguria (%)</td>
<td>78.0</td>
<td>78.1</td>
<td>0.97</td>
</tr>
<tr>
<td>Pre-randomization RRT (%)</td>
<td>65.8</td>
<td>65.4</td>
<td>0.54</td>
</tr>
<tr>
<td>BUN at initiation of RRT</td>
<td>65.9±30.2</td>
<td>66.7±35.2</td>
<td>0.68</td>
</tr>
</tbody>
</table>
60-Day All Cause Mortality

- Odds Ratio: 1.09
- 95% CI: 0.86-1.40
- P=0.47

60-Day All Cause Mortality: Subgroup Analysis

<table>
<thead>
<tr>
<th>Statistic (95% CI)</th>
<th>Intensive Management (N=563)</th>
<th>Less-Intensive Management (N=561)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>288 (51.2)</td>
<td>269 (48.0)</td>
<td>1.15 (0.90-1.47)</td>
</tr>
<tr>
<td>Discharged to home off dialysis by day 40</td>
<td>88 (15.7)</td>
<td>92 (16.4)</td>
<td>0.95 (0.68-1.32)</td>
</tr>
<tr>
<td>Recovery of kidney function by day 28</td>
<td>0.03 (0.02-0.07)</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>Complete recovery</td>
<td>85 (15.4)</td>
<td>102 (18.4)</td>
<td></td>
</tr>
<tr>
<td>Partial recovery</td>
<td>49 (8.9)</td>
<td>58 (9.0)</td>
<td></td>
</tr>
<tr>
<td>No recovery</td>
<td>419 (75.8)</td>
<td>403 (72.6)</td>
<td></td>
</tr>
</tbody>
</table>
### Management of IHD

<table>
<thead>
<tr>
<th></th>
<th>Intensive Management (N=563)</th>
<th>Less-Intensive Management (N=561)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatments per week (95% CI)</td>
<td>5.4 (5.2-5.6)</td>
<td>3.0 (2.8-3.3)</td>
</tr>
<tr>
<td>Interval between treatments (days, 95% CI)</td>
<td>1.1 (1.1-1.2)</td>
<td>2.1 (2.0-2.2)</td>
</tr>
<tr>
<td>Median treatment length (hours, IQR)</td>
<td>4.0 (3.3-4.5)</td>
<td>4.0 (3.5-4.5)</td>
</tr>
<tr>
<td>Blood flow rate (mL/min)</td>
<td>360±69</td>
<td>360±62</td>
</tr>
<tr>
<td>Dialysate flow rate (mL/min)</td>
<td>730±123</td>
<td>710±135</td>
</tr>
<tr>
<td>Net ultrafiltration (L.)</td>
<td>3.7±1.2</td>
<td>2.1±1.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>pre-dialysis</th>
<th>post-dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN</td>
<td>45±23</td>
<td>70±33</td>
</tr>
<tr>
<td>Kt/V urea</td>
<td>16±12</td>
<td>25±15</td>
</tr>
</tbody>
</table>

#### Other studies in support of this result?

- Single center study of dose of CVVHDF
- 20 cc/kg/hour vs 35 cc/kg/hour
- 100 patients/arm
ANZICS RENAL Study

- "Closed" ICU model where intensivists prescribe RRT
- RCT of 2 doses of CVVHDF: 25 vs 40 ml/kg/hour of effluent
- Targeted enrollment of 1500 patients: power calculations based on mortality rate of 60% in control arm, 51.5% in intervention arm

Conclusions

- Interventions to prevent acute renal failure remain limited ("best standard care")
- Avoid nephrotoxins, including oral sodium phosphate bowel preps and hydroxyethylstarch
- Nephrogenic systemic fibrosis has been reported after gadolinium administration in AKI, though it is rare

Conclusions

- Diuretics can be used to control volume overload in patients with AKI, but would have low threshold to initiate dialysis if needed for volume removal
- Higher intensity dialysis does not have mortality benefit in two (three) recently completed randomized clinical trials
- Need to pay attention to the delivered dose of dialysis to ensure "adequacy"