OUTCOMES IN PATIENTS WITH ACUTE KIDNEY INJURY ARE IMPROVED BY EARLY INITIATION OF RENAL REPLACEMENT THERAPY

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Presentation Overview

- Background / Definitions
- History
- Indications for initiation of therapy
- Outcomes Studies
- Conclusions
- Questions
Acute Kidney Injury (AKI)
- Rapid decline in glomerular filtration rate (GFR), resulting in the disturbance of renal physiological functions:
  - Impairment of nitrogenous waste product excretion
  - Loss of water and electrolyte regulation
  - Loss of acid-base regulation
- RIFLE criteria

Renal Replacement Therapy (RRT)
- Intermittent hemodialysis (iHD)
- Continuous renal replacement therapies (CRRTs)
- Hybrid therapies: sustained low-efficiency dialysis (SLED)
History

- Concept first proposed by Graham in 1854
- Introduced into clinical practice in the 1940s and early 1950s
- Initially used to principally treat the advanced symptoms of renal failure
- Early technology did not clearly lower acute mortality
- Given the severity of illness and the lack of advanced critical care medicine during this period, patients acutely died of complications
The Machines

Images from: Home Dialysis Central, Advanced Renal Education, and Gambro
Indications for Initiation of RRT

- Refractory fluid overload
- Azotemia
- Increased creatinine
- Decreased urine output
- Creatinine clearance
- Hyperkalemia or rapidly rising potassium levels
- Metabolic acidosis
- Signs of uremia
### Overview of Studies

Table 2. Summary of studies evaluating the timing of initiation of renal replacement therapy (RRT)

<table>
<thead>
<tr>
<th>Study</th>
<th>Yr</th>
<th>Mode of RRT</th>
<th>Study Design</th>
<th>No.</th>
<th>Criteria for Initiation of RRT</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td>Early</td>
<td>Survive (%)</td>
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<td></td>
<td></td>
<td>Late</td>
<td>Survive (%)</td>
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<td>Early</td>
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<tr>
<td>S&lt;sub&gt;Cr&lt;/sub&gt; &lt; 5 mg/dL</td>
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<td></td>
<td>S&lt;sub&gt;Cr&lt;/sub&gt; &gt; 5 mg/dL</td>
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</tr>
<tr>
<td>S&lt;sub&gt;Cr&lt;/sub&gt; &gt; 10 mg/dL or clinical indications</td>
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<tr>
<td>Treatment goal: BUN &lt; 60 mg/dL, S&lt;sub&gt;Cr&lt;/sub&gt; &lt; 5 mg/dL</td>
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<td></td>
<td></td>
<td>S&lt;sub&gt;Cr&lt;/sub&gt; &gt; 9 mg/dL</td>
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<tr>
<td>meeting AKI definition</td>
<td></td>
<td></td>
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<td></td>
<td>S&lt;sub&gt;K&lt;/sub&gt; &gt; 6.5 mmol/L, or pulmonary edema</td>
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<td></td>
<td></td>
<td>HV: 74</td>
</tr>
<tr>
<td>Demirkiliç et al (26)</td>
<td>2004</td>
<td>CRRT</td>
<td>Retrospective</td>
<td>61</td>
<td>UOP &lt; 100 mL/8 hr</td>
<td>77</td>
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<td></td>
<td></td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>Elahi et al (27)</td>
<td>2004</td>
<td>CRRT</td>
<td>Retrospective</td>
<td>64</td>
<td>UOP &lt; 100 mL/8 hr</td>
<td>78</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>57</td>
</tr>
<tr>
<td>Piccinni et al (28)</td>
<td>2006</td>
<td>CRRT</td>
<td>Retrospective</td>
<td>80</td>
<td>&lt;12 hrs after ICU admission</td>
<td>55</td>
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<td></td>
<td>28</td>
</tr>
</tbody>
</table>

IHD, intermittent hemodialysis; CRRT, continuous renal replacement therapy; RCT, randomized controlled trial; BUN, blood urea nitrogen; S<sub>Cr</sub>, serum creatinine; AKI, acute kidney injury; UOP, urine output; ICU, intensive care unit; S<sub>K</sub>, serum potassium; LV, low-volume hemofiltration; HV, high-volume hemofiltration.
Early Studies

Four of the five studies showed improved survival with early initiation of RRT.

Gillum examined intensity of dialysis, not timing.

Published in 1961 through 1986.

Outcomes based on primitive technology & understanding.

Many innovations since studies performed.

Table 2. Summary of studies evaluating the timing of initiation of renal replacement therapy (RRT)

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<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parsons et al (20)</td>
<td>1961</td>
<td>IHD</td>
<td>Retrospective</td>
<td>33</td>
<td>BUN 120–150 mg/dL, BUN &gt;200 mg/dL</td>
<td>Early: 75, Late: 12</td>
</tr>
<tr>
<td>Fischer et al (21)</td>
<td>1966</td>
<td>IHD</td>
<td>Retrospective</td>
<td>162</td>
<td>BUN ~150 mg/dL, BUN &gt;200 mg/dL</td>
<td>Early: 43, Late: 26</td>
</tr>
<tr>
<td>Kleinmanet et al (22)</td>
<td>1972</td>
<td>IHD</td>
<td>Retrospective</td>
<td>500</td>
<td>BUN &lt;93 mg/dL, BUN &lt;183 mg/dL</td>
<td>Early: 73, Late: 58</td>
</tr>
</tbody>
</table>

Treatment goal:
- \( S_{\text{Cr}} < 5 \text{ mg/dL} \)
- \( S_{\text{Cr}} < 9 \text{ mg/dL} \)
Outcomes Study #1

- **Design:**
  - Retrospective analysis

- **Arms:**
  - Early initiation (BUN<60mg/dl)
  - Late initiation (BUN>60mg/dl)

- **Outcomes:**
  - Length of hospital stay
  - Duration of RRT
  - Recovery of renal function
  - Overall survival

Gettings et al. 1999
Outcomes Study #1 (cont.)

- **Results:**
  - No significant difference between groups in:
    - Length of hospital stay
    - Duration of RRT
    - Recovery of renal function
  - Significant difference between groups in:
    - Survival
      - 39% in early initiation group
      - 20.3% in late initiation group
  - *p = 0.041* (Gettings et al. 1999)
Outcomes Study #2

- **Design:**
  - Multicenter observational

- **Study Arms:**
  - Low degree of azotemia (BUN<76mg/dl)
  - High degree of azotemia (BUN>76mg/dl)

- **Outcomes:**
  - Risk of death within 60 days from diagnosis of AKI

Median BUN of all study participants
Outcomes Study #2 (cont.)

Results:

- Crude survival rates lower if RRT started at higher BUN ($p = 0.09$)
- Relative risk for death associated with late RRT = 1.85 (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>14 day survival</th>
<th>28 day survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early RRT</td>
<td>80%</td>
<td>65%</td>
</tr>
<tr>
<td>Late RRT</td>
<td>75%</td>
<td>59%</td>
</tr>
</tbody>
</table>

Liu et al. 2006
Outcomes Study #3

- **Design:**
  - Randomized, controlled, two-center study

- **Study Arms:**
  - Early high-volume RRT
  - Early low-volume RRT
  - Late low-volume RRT

- **Outcomes:**
  - Primary:
    - 28 day survival
    - Recovery of renal function
  - Secondary:
    - ICU survival
    - Hospital survival
    - Duration of mechanical ventilation
    - Length of ICU stay
    - Length of hospitalization

Bouman et al. 2002
Outcomes Study #3 (cont.)

- Results:
  - No significant difference in recovery of renal function between all groups
  - No significant survival difference between all groups
  - 100% recovery of renal function in survivors
  - “We could not show a significant survival benefit for early hemofiltration or high filtration rates; however, no deleterious effects were seen either”
Outcomes Study #4

- **Design:**
  - Prospective, multinational, multicenter observational cohort

- **Arms:**
  - Early vs. late RRT:
    - Serum biomarkers (urea & creatinine)
    - Change in biomarkers from ICU admit to initiation of RRT
    - RRT initiation relative to ICU admit date

- **Outcomes:**
  - Hospital survival
  - Renal recovery
  - Duration of RRT
  - Length of ICU & hospital stay

Bagshaw et al. 2008
Results:
- Mortality differences depend on how timing is defined
- Late initiation of RRT associated with:
  - Longer duration of RRT
  - Longer hospital stay
  - Increased risk of dialysis dependence as an outpatient

Bagshaw et al. 2008
### Outcomes Study #4 (cont.)

<table>
<thead>
<tr>
<th></th>
<th>Duration of RRT (days)</th>
<th>Hospital Stay (days)</th>
<th>Risk of Dialysis Dependence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>$p=0.004$</td>
<td>$p&lt;0.001$</td>
<td>$p&lt;0.0001$</td>
</tr>
<tr>
<td>Creatinine</td>
<td>$p=0.06$</td>
<td>NS</td>
<td>$p&lt;0.0001$</td>
</tr>
<tr>
<td>Change in Urea/Cr</td>
<td>$p=0.01$</td>
<td>$p&lt;0.001$</td>
<td>NS</td>
</tr>
<tr>
<td>Time of RRT Initiation</td>
<td>$p&lt;0.001$</td>
<td>$p&lt;0.001$</td>
<td>NS</td>
</tr>
</tbody>
</table>

Bagshaw et al. 2008
Research Issues to Address

- Indicators of AKI:
  - Metabolic abnormalities
  - Acidosis
  - Anuria/oliguria
  - Fluid status

- RRT initiation timing:
  - Admission
  - Start of ICU level care
  - Initial insult
  - Critical level of indicators

- Markers of therapy:
  - Creatinine
  - Urea

- Study size/power
Proposed Research Method

- **Arms:**
  - RRT within 24 hours of AKI diagnosis vs. RRT per conventional indications at MD discretion

- **Inclusion:**
  - >17 year old, ICU admit, stage III AKI, intent to continue life supporting measures

- **Exclusion:**
  - <17, hepatic failure, burns, cardiac surgery, not fully committed to continue life supporting measures

- **N = 1600**

- All patients receive RRT:
  - Discontinued when creatinine clearance >20 ml/min or per MD

- **Endpoints:**
  - Hospital survival and return of renal function

Gibney et al. 2008
Conclusions

- Limited number of randomized controlled trials
- Many non-standardized definitions, parameters, outcomes, etc.
- Almost all studies show equivocal or improved outcomes with early RRT

Early initiation of RRT has been shown to improve outcomes in many (but not all) measures of AKI. Given the significant benefits, and limited risks, it should be the current standard of care.
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