ACUTE RENAL SUPPORT THERAPY:
SURVIVAL & RENAL RECOVERY – MAXIMIZING OUTCOMES

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Disclosures

- **Prior Member:** ASN AKI Advisory Group

- **Prior Advisory Board:**
  - CR Bard, Inc
  - Baxter, Inc - Acute Kidney Injury + CRRT (non-compensated)

- **Current research collaboration:**
  - Potrero, Inc

- **Wife (Emory faculty):** no conflicts of interest
Goals & Outline

Goals:
- Describe frequency & impact of AKI
- Describe outcomes of CRRT vs IRRT vs PIRRT
- Describe “optimal” CRRT

Outline:
- AKI epidemiology & mortality
- CRRT outcome review
- Optimal CRRT
  - Timing of acute RRT
Case

- 37 yo M presents with acute onset of severe abdominal pain with SOB. In ED, noted to have profound epigastric tenderness, firm abdomen. HR 128, BP 85/45, temp 38.1

- **Initial labs:**
  - Calcium 8.4
  - Lipase 1100
  - AST 40, ALT 52

- **CT Abd/pelvis:** marked inflammation of pancreas with no evidence of pancreatic necrosis
Admitted to ICU. Aggressive volume resuscitation with 10L NS over the next 24 hrs
- BP improved to 105/58 but dependent low dose norepi @ 0.05 mcg/kg/min
- UOP only 120cc since admission

Labs:

- pH 7.22/48/88 with lactic acid 3.5 on 50% ventimask

Progressive resp distress secondary to worsening pulmonary infiltrates (ARDS), abd pain and distention requiring intubation
Case - Questions

- Does AKI impact pt’s outcomes?
- Does patient need RRT now?
- How to provide RRT?
Mortality – Questions

- Over the last 50 years, rapid advance in technology to perform RRT (RST) in critically ill with AKI

- Obviously, providing a mortality benefit with RRT
  - Historical mortality figures for AKI exceed 90% before RRT
  - Bagshaw meta-analysis (2008)
    - Overall mortality = 63.2% in CRRT & 63.8% in IHD

- Why are the patients still dying at such an alarming rate?
  - Are we performing “good” or “optimal” RRT?
Potential Measured Outcomes

- Mortality
- Renal Recovery
  - Prolonged or permanent dialysis dependency
- Time on ventilator, in ICU, in hospital, etc
- Volume control
- Hemodynamic stability/effects
  - Vasopressor doses
- Therapy complications
  - Access
  - Bleeding
  - Clotting
- Cost
Mortality – IHD vs CRRT

Mortality – IHD vs CRRT

Bagshaw et al. CCM. 2008;36(2):610-617. PMID#: 18216610
3 meta-analyses reaching same **statistical** result:
- **no difference** in mortality between intermittent & continuous RRT in critically ill patients with AKI requiring RRT

Authors reached divergent conclusions
- Bagshaw & Cochrane stating that unable to recommend one modality preferentially based on data
- Pannu argues that alternate-day IHD should be preferred given equivalent mortality & lower costs
Mortality – IHD vs CRRT

- Single center, RCT in **medical ICU** comparing:
  - CVVH (35ml/kg/hr)
  - IHD (4hrs, $Q_b = 200-250 \text{ ml/min}$, $Q_d = 500 \text{ ml/min}$)
  - Anticoag: heparin (> 95%)


- Goal: > 200 per arm

- **Stopped early** because: “[There] was a major change in RRT equipment & procedures that was beyond the investigators’ control. With the ICU team confronted with new machinery & new treatment protocols ([i.e] automated citrate anticoagulation, preference for HDF instead of HD), it became obvious that this would introduce an unacceptable bias to the trial. The investigators therefore decided to terminate the study prematurely.”
Mortality – CRRT vs PIRRT

- Single center, RCT in surgical ICU comparing:
  - Pre-dilution CVVH (35ml/kg/hr, blood flow 100-120 ml/min)
  - SLED (12-hrs, Qb = 100-120 ml/min, Qd = 120-140 ml/min)


<table>
<thead>
<tr>
<th>Table 3 Primary and secondary outcomes.</th>
<th>All (n = 232)</th>
<th>SLED (n = 115)</th>
<th>CVVH (n = 117)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from any cause by day 90</td>
<td>122 (52.6 %)</td>
<td>57 (49.6 %)</td>
<td>65 (55.6 %)</td>
<td>0.434**</td>
</tr>
<tr>
<td>Death from any cause up to 30 August 2009</td>
<td>155 (66.8 %)</td>
<td>76 (66.1 %)</td>
<td>79 (67.5 %)</td>
<td>0.926**</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>119 (51.3 %)</td>
<td>57 (49.6 %)</td>
<td>62 (53.0 %)</td>
<td>0.696**</td>
</tr>
<tr>
<td>Mortality in ICU</td>
<td>98 (42.2 %)</td>
<td>49 (42.6 %)</td>
<td>49 (41.9 %)</td>
<td>0.984**</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>205 (88.4 %)</td>
<td>101 (87.8%)</td>
<td>104 (88.9%)</td>
<td>0.962**</td>
</tr>
<tr>
<td>Days of mechanical ventilation</td>
<td>1.94 ± 19.7</td>
<td>17.7 ± 19.4</td>
<td>20.9 ± 19.8</td>
<td>0.047*</td>
</tr>
<tr>
<td>Days in intensive care unit</td>
<td>21.7 ± 21.1</td>
<td>19.6 ± 20.1</td>
<td>23.7 ± 21.9</td>
<td>0.038*</td>
</tr>
</tbody>
</table>

- RRT costs/day (acquisition cost for the Genius and water preparation device included with €8/treatment. Number of membranes used per treatment were considered)
  - SLED (using a high-flux membrane): €63.2
  - SLED (using an AKI membrane): €206.7
  - CVVH: €209.3

- Overall modality costs per treatment (nursing included, without technician, physician and other medical staff)
  - SLED: €96.8
  - CVVH: €240.4
  - P: €258.9

- Reimbursement for modality/day (German DRG system)
  - SLED: €221.0
  - CVVH: €221.0
  - DRG: €300.0
CVVH vs EDHF

- Retrospective study – 145 patients with sepsis induced AKI treated with either CVVH versus EDHF (extended daily HF)
  - CRRT group had higher proportion of “septic shock” AND EDHF group had higher proportion of “severe sepsis”
  - Avg MAP at initiation: CRRT 65.2 & EDHF 73.7 (p = 0.037)
  - APACHE 2 & SOFA scores equivalent

<table>
<thead>
<tr>
<th>Primary outcome, n (%)</th>
<th>CVVH (n=65)</th>
<th>EDHF (n=80)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal recovery-60 days</td>
<td>33 (50.77)</td>
<td>26 (32.50)</td>
<td>0.026</td>
</tr>
<tr>
<td>Mortality-60 days</td>
<td>29 (44.62)</td>
<td>37 (46.25)</td>
<td>0.844</td>
</tr>
</tbody>
</table>
Possible Explanations – why?

- There really is **no** difference in survival
- There **is** a difference – studies have not demonstrated/detected difference in survival
- Not providing “optimal CRRT” at the time
  - Dose, mode, timing of initiation, anticoagulation, nutrition, medication dosing, volume control, etc
  - Competing influences on mortality
Trial Limitations

- **Study design limits generalizability**
  - Heterogeneous study designs

- **Inconsistent CRRT operating characteristics**
  - Mode
  - Dose
  - Anticoagulation
  - Timing of Initiation

- **Power calculations & assumptions**
  - Studies have not been adequately powered to show small changes in mortality

- **Sicker patient population receiving CRRT** (usually)
  - Difficulties with randomization/recruitment
  - Cross-over complicates analyses
Role of CRRT?

- If there is no improvement in survival, is there a role for CRRT?

- Does CRRT provide superior performance on any other outcomes?

- Can/should we accept that CRRT & IHD are equivalent? Can we accept as true that there is no difference between CRRT & IHD?
Hemodynamic Effects of RRT: Cochrane Review – IHD vs CRRT


MAP @ end of study period

Escalation of vasopressors
Volume Control

- CRRT provides **superior control of volume overload** compared to IHD in multiple clinical scenarios.
  - AKI
  - ADHF
  - Liver failure
  - Shock
  - Respiratory failure
Volume Control with RRT: Modality matters


IUF versus SCUF in ADHF


![Graph showing comparison between IUF and SCUF in ADHF](image)
Renal Recovery Rates

- **CKD after AKI is common**
  - 30-80% in adults/pediatric populations (long-term follow up & database studies)
  - Not necessarily dialysis dependent but can be progressive

- Implications of *ESRD after AKI*
  - Decreased quality of life
  - Higher mortality/worse long-term outcomes
  - High costs & consumption of resources
ESRD after AKI – Mortality

Bhandari & Turney. QJM. 1996;89(6):415-21. PMID#: 8758044
Renal Recovery Rates

- Swedish cohort
  - 32 ICUs 1999-2004
  - Prospective data collection in national database

- 2202 patients analyzed

- OR for ESRD after IHD (compared to CRRT) $= 2.60$
  (95% CI 1.5-4.3)

Bell et al. ICM. 2007;33(5):773-80. PMID#: 17364165
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IRRT Events</th>
<th>IRRT Total</th>
<th>CRRT Events</th>
<th>CRRT Total</th>
<th>Weight</th>
<th>M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.1.1 Observational</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Andrikos 2009</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>33</td>
<td>1.5%</td>
<td>1.65 [0.25, 10.81]</td>
<td></td>
</tr>
<tr>
<td>Bagshaw 2006</td>
<td>15</td>
<td>42</td>
<td>12</td>
<td>54</td>
<td>7.0%</td>
<td>1.61 [0.84, 3.06]</td>
<td></td>
</tr>
<tr>
<td>Bell 2007</td>
<td>26</td>
<td>158</td>
<td>78</td>
<td>944</td>
<td>9.8%</td>
<td>1.99 [1.32, 3.00]</td>
<td></td>
</tr>
<tr>
<td>CartinCeba 2009</td>
<td>256</td>
<td>555</td>
<td>26</td>
<td>229</td>
<td>10.3%</td>
<td>4.06 [2.80, 5.90]</td>
<td></td>
</tr>
<tr>
<td>Chang 2004</td>
<td>4</td>
<td>44</td>
<td>1</td>
<td>11</td>
<td>1.3%</td>
<td>1.00 [0.12, 8.08]</td>
<td></td>
</tr>
<tr>
<td>Elsevier 2010</td>
<td>37</td>
<td>175</td>
<td>13</td>
<td>98</td>
<td>7.7%</td>
<td>1.59 [0.89, 2.85]</td>
<td></td>
</tr>
<tr>
<td>Garcia–Fernandes 2011</td>
<td>0</td>
<td>16</td>
<td>0</td>
<td>55</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Gonwa 2001</td>
<td>1</td>
<td>6</td>
<td>4</td>
<td>25</td>
<td>1.4%</td>
<td>1.04 [0.14, 7.71]</td>
<td></td>
</tr>
<tr>
<td>Jacka 2005</td>
<td>9</td>
<td>14</td>
<td>3</td>
<td>24</td>
<td>3.5%</td>
<td>5.14 [1.66, 15.89]</td>
<td></td>
</tr>
<tr>
<td>Lin 2009</td>
<td>11</td>
<td>54</td>
<td>10</td>
<td>83</td>
<td>5.7%</td>
<td>1.69 [0.77, 3.71]</td>
<td></td>
</tr>
<tr>
<td>Lins 2006</td>
<td>9</td>
<td>37</td>
<td>1</td>
<td>4</td>
<td>1.6%</td>
<td>0.97 [0.16, 5.83]</td>
<td></td>
</tr>
<tr>
<td>Marshall 2012</td>
<td>5</td>
<td>56</td>
<td>2</td>
<td>16</td>
<td>2.1%</td>
<td>0.71 [0.15, 3.34]</td>
<td></td>
</tr>
<tr>
<td>Park 2005</td>
<td>37</td>
<td>83</td>
<td>1</td>
<td>9</td>
<td>1.5%</td>
<td>4.01 [0.62, 25.86]</td>
<td></td>
</tr>
<tr>
<td>Swartz 2005</td>
<td>24</td>
<td>110</td>
<td>10</td>
<td>64</td>
<td>6.7%</td>
<td>1.40 [0.71, 2.73]</td>
<td></td>
</tr>
<tr>
<td>Uchino 2007</td>
<td>37</td>
<td>110</td>
<td>52</td>
<td>360</td>
<td>10.5%</td>
<td>2.33 [1.62, 3.35]</td>
<td></td>
</tr>
<tr>
<td>Waldrop 2005</td>
<td>7</td>
<td>12</td>
<td>6</td>
<td>14</td>
<td>5.8%</td>
<td>1.36 [0.63, 2.94]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>479</td>
<td>1476</td>
<td>224</td>
<td>2023</td>
<td>76.4%</td>
<td>1.99 [1.53, 2.59]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>479</td>
<td>1476</td>
<td>224</td>
<td>2023</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.09; \text{Chi}^2 = 24.14, \text{df} = 14 (P = 0.04); I^2 = 42\% 
Test for overall effect: \( Z = 5.14 (P < 0.00001) \)

<table>
<thead>
<tr>
<th><strong>1.1.2 RCT</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Abe 2010</td>
</tr>
<tr>
<td>Augustine 2004</td>
</tr>
<tr>
<td>Kumar 2004</td>
</tr>
<tr>
<td>Lins 2009</td>
</tr>
<tr>
<td>Mehta 2001</td>
</tr>
<tr>
<td>Uehlinger 2005</td>
</tr>
<tr>
<td>Vinsonneau 2006</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
</tr>
<tr>
<td>Total events</td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.00; \text{Chi}^2 = 3.20, \text{df} = 6 (P = 0.78); I^2 = 0\% 
Test for overall effect: \( Z = 0.71 (P = 0.48) \)

<table>
<thead>
<tr>
<th><strong>Total (95% CI)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1716</td>
</tr>
<tr>
<td>2255</td>
</tr>
<tr>
<td>100.0%</td>
</tr>
<tr>
<td>1.73 [1.35, 2.20]</td>
</tr>
<tr>
<td>517</td>
</tr>
<tr>
<td>256</td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.12; \text{Chi}^2 = 37.19, \text{df} = 21 (P = 0.02); I^2 = 44\% 
Test for overall effect: \( Z = 4.36 (P < 0.00001) \)
Test for subgroup differences: \( \text{Chi}^2 = 5.45, \text{df} = 1 (P = 0.02), I^2 = 81.7\% \)
Debate Continues: IHD vs CRRT vs PIRRT

- Volume overload, renal recovery, shock all independently associated with mortality
  - If CRRT improves these factors, why do we not see a survival benefit?

- AKI has many direct & indirect effects on homeostasis & end-organ function
  - RRT (RST) might not affect these other contributors to mortality
What is Good/Optimal CRRT?

- **Clarity regarding some issues**
  - Dosing targets
    - **No benefit** of “high” dose (>35ml/kg/hr) in *most* patients
    - Minimal effective dose (floor) = **20ml/kg/hr** (delivered dose)
  - Anticoagulation strategies – Citrate preferred
  - Vascular access – deep R IJ preferred, longer catheters

- **Improving knowledge concerning (but still incomplete):**
  - Drug dosing – especially antimicrobials
  - Nutrition support in CRRT
  - Timing & target of initiation?
    - Indication? → BUN/Cr, volume, acid/base, electrolytes, time, other

- Many important *unanswered* questions
  - Filter membrane material
  - Mode – convection vs diffusion vs both
  - Hybrid therapies (PIRRT/SLED)
Key Issues – Acute RRT for AKI

- When should **acute RRT** therapy be initiated?

- What are the critical elements for the delivery of **successful high-quality acute RRT**?
  - Type of technique
  - Dose of RRT
  - Anticoagulation
  - Vascular Access
Acute RRT – Early vs Delayed

**THEORETICAL ADVANTAGES**

- Uremic/metabolic control
- Improved fluid management & prevention of fluid overload
- Acid-base homeostasis
- Non-renal organ function
- “Unloading” or “resting” stressed and damaged kidneys
- Improved clinical outcomes (i.e. survival)?

**THEORETICAL DISADVANTAGES**

- Infectious/mechanical complications of catheter
- Bioincompatibility
- Bleeding related to anticoagulation
- Risk of hypotension and decreased renal recovery
- Potential loss of essential substances (nutrients, drugs)
- Cost
5.1.1: Initiate RRT emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist. (Not Graded)

5.1.2: Consider the broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests—rather than single BUN and creatinine thresholds alone—when making the decision to start RRT. (Not Graded)
Artificial Kidney Initiation in Kidney Injury (AKIKI) Trial [multicenter, France]

- Inclusion criteria (all must be present):
  - Adult, admission to an ICU + AKI compatible with ATN
  - Patients **must be receiving invasive mechanical ventilation or catecholamine infusion**
  - At least one of the following: serum creatinine > 4.0 mg/dL or greater than 3 X baseline creatinine, anuria for > 12 hrs, oliguria (UO <0.3 ml/kg/h or < 500 ml/day) for > 24 hrs (KDIGO Stage 3)

- “Early” RRT is initiated < 6 hrs after documentation of above criteria

- “Delayed” RRT is initiated if one of the following occur:

<table>
<thead>
<tr>
<th>Table S1. Criteria mandating RRT initiation in the delayed RRT strategy group*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oliguria or anuria for more than 72 hours after randomization</td>
</tr>
<tr>
<td>Blood urea nitrogen of more than 112 md/dl (40 mmol/liter)</td>
</tr>
<tr>
<td>Serum potassium concentration of more than 6 mmol/liter</td>
</tr>
<tr>
<td>Serum potassium concentration of more than 5.5 mmol/liter</td>
</tr>
<tr>
<td>pH below 7.15 in a context of pure metabolic acidosis (PaCO₂ below 35 mmHg) or in a context of mixed acidosis with PaCO₂ of 50 mmHg or more without possibility of increasing alveolar ventilation</td>
</tr>
<tr>
<td>Acute pulmonary edema due to fluid overload responsible for severe hypoxemia requiring oxygen flow rate of more than 5 l/min to maintain an SpO₂ of more than 95% or requiring an FiO₂ greater than 50% in patients already on invasive or non-invasive mechanical ventilation and despite diuretic therapy</td>
</tr>
</tbody>
</table>

Gaudry et al. NEJM. 2016 Jul 14;375(2):122-33. PMID #: 27181456
AKIKI Trial Results

Gaudry et al. NEJM. 2016 Jul 14;375(2):122-33. PMID #: 27181456
AKIKI Results – Notable findings

- IHD was the initial mode of RRT in 55% of RRT cases
- CRRT was the sole RRT in only 30% of RRT cases
- Patients who did not receive RRT had the lowest severity-of-illness scores at baseline

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### Overall Mortality of Cohort

<table>
<thead>
<tr>
<th></th>
<th>Early RRT (n=311)</th>
<th>Delayed – RRT (n=157)</th>
<th>Delayed – NO RRT (n=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>48.5%</td>
<td>61.8%</td>
<td>37.1%</td>
</tr>
</tbody>
</table>

Gaudry et al. NEJM. 2016 Jul 14;375(2):122-33. PMID #: 27181456
Early vs. late initiation of RRT in critically ill patients with AKI (ELAIN) trial [single center, Germany]

250 patients with inclusion criteria:

- **KDIGO stage 2** (two-fold increase in serum creatinine from baseline and/or urinary output <0.5 ml/kg/h ≥12 h) **despite optimal resuscitation**
- Plasma neutrophil gelatinase-associated lipocalin (NGAL) >150 ng/ml
- One of the following: a) severe sepsis; b) use of catecholamines; c) refractory fluid overload (worsening pulmonary edema, PaO2/FiO2 < 300 mmHg and/or fluid balance >10 % of body weight); and d) development or progression of nonrenal organ dysfunction (Sequential Organ Failure Assessment (SOFA) score ≥2);
- Age between 18 and 90 years
- Intention to provide full intensive care treatment for at least 3 days

“**Early**” RRT = within **8 hrs** of **stage 2 AKI** & inclusion criteria

“**Delayed**” RRT = within **12 hrs** of **stage 3 AKI** or an absolute indication \([BUN>100 \text{ mg/dL}, \text{potassium}>6 \text{ meq/L, magnesium}>8 \text{ meq/L, severe oliguria} (<200\text{ml/12 hrs OR anuria}), \text{OR diuretic resistant organ edema}]\)
**ELAIN Trial**

**Intervention:**
- 1:1 randomization stratified by SOFA CV score (0-2 vs 3-4) AND oliguria

**RRT Treatments** – once RRT initiated:
- CVVHDF, total effluent rate 30 ml/kg/hr (excluding fluid removal rate), 1:1 pre-filter replacement: dialysate, RCA

**RRT cessation criteria** – required both:
- UOP > 400 ml/24hrs without OR > 2100 ml/24hrs with diuretics
- Creatinine clearance > 20 ml/min

If still **dependent on RRT after 7 days**, CRRT **could** be changed to PIRRT (SLEDD), SCUF, or IHD at discretion of treatment team.

Zarbock A et al. JAMA. 2016 May 24-31;315(20):2190-9. PMID #: 27209269
Table 2. Patient Characteristics at the Time of Renal Replacement Therapy (RRT) Initiation

<table>
<thead>
<tr>
<th></th>
<th>Early (n = 112)</th>
<th>Delayed (n = 119)</th>
<th>Absolute Difference Early vs Delayed (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received RRT, No.</td>
<td>112</td>
<td>108</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from meeting eligibility criteria to randomization, median (Q1, Q3), h</td>
<td>2.0 (1.0, 3.0)</td>
<td>2.0 (1.0, 3.0)</td>
<td>0.0 (0.0 to 0.0)</td>
<td>.36</td>
</tr>
<tr>
<td>Time from KDIGO 2 to RRT, mean (SD), h</td>
<td>5.4 (2.2)</td>
<td>40.0 (54.5)</td>
<td>-34.5 (-45.0 to -24.0)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Figure 2. Mortality Probability Within 90 Days After Study Enrollment for Patients Receiving Early and Delayed Initiation of Renal Replacement Therapy (RRT)

Inverse normal log-rank test, P = .03; HR = 0.66 (95% CI, 0.45-0.97)

## ELAIN Trial – Results

Zarbock A et al. JAMA. 2016 May 24-31;315(20):2190-9. PMID #: 27209269

### Table 3. Clinical Outcomes for Early vs Delayed Renal Replacement Therapy (RRT) Among Critically Ill Patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Early (n = 112)</th>
<th>Delayed (n = 119)</th>
<th>P Value</th>
<th>Absolute Difference, % (95% CI)</th>
<th>OR or HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome, No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90-d All-cause mortality</td>
<td>44 (39.3)</td>
<td>65 (54.7)</td>
<td>.03</td>
<td>−15.4 (−28.1 to −2.6)</td>
<td>HR: 0.66 (0.45 to 0.97)</td>
</tr>
</tbody>
</table>

### Selected Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Early (n = 112)</th>
<th>Delayed (n = 108)</th>
<th>P Value</th>
<th>Absolute Difference, % (95% CI)</th>
<th>OR or HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of RRT, median (Q1, Q3), d&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9 (4, 44)</td>
<td>25 (7, &gt;90)</td>
<td>.04</td>
<td>−18 (−41 to 4)</td>
<td>HR: 0.69 (0.48 to 1.00)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>ICU stay, median (Q1, Q3), d</td>
<td>15.5 (8.0, 28.0)</td>
<td>16.0 (6.8, 30.0)</td>
<td>.95</td>
<td>0.0 (−3.0 to 3.0)</td>
<td></td>
</tr>
<tr>
<td>ICU stay, median (Q1, Q3), d&lt;sup&gt;i&lt;/sup&gt;</td>
<td>19 (9, 29)</td>
<td>22 (12, 36)</td>
<td>.33</td>
<td>−3.0 (−12.0 to 4.5)</td>
<td>HR: 0.85 (0.61 to 1.19)&lt;sup&gt;m&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hospital stay, median (Q1, Q3), d</td>
<td>33.0 (18.0, 58.0)</td>
<td>43.0 (19.5, 81.3)</td>
<td>.05</td>
<td>−9.0 (−19.0 to 0.0)</td>
<td></td>
</tr>
<tr>
<td>Hospital stay, median (Q1, Q3), d&lt;sup&gt;n&lt;/sup&gt;</td>
<td>51 (31, 74)</td>
<td>82 (67, &gt;90)</td>
<td>&lt;.001</td>
<td>−37 (−∞ to −19.5)</td>
<td>HR: 0.34 (0.22 to 0.52)&lt;sup&gt;o&lt;/sup&gt;</td>
</tr>
<tr>
<td>Duration of mechanical ventilation, median (Q1, Q3), h</td>
<td>125.5 (41, 203)</td>
<td>181.0 (65, 413)</td>
<td>.002</td>
<td>−60.0 (−110.0 to −22.0)</td>
<td></td>
</tr>
<tr>
<td>Characteristic</td>
<td>AKIKI Trial</td>
<td>ELAIN Trial</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>--------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sites</td>
<td>31 (France)</td>
<td>1 (Germany)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of participants</td>
<td>620</td>
<td>231</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early RRT definition</td>
<td>KDIGO stage 3</td>
<td>KDIGO stage 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed RRT definition</td>
<td>Absolute indications</td>
<td>KDIGO stage 3 OR absolute indication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SOFA score</td>
<td>10.8 +/- 3.2</td>
<td>15.8 +/- 2.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical vs surgical</td>
<td>80% medical/20% surgical</td>
<td>93% surgical (cardiac/abdominal)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative Fluid balance</td>
<td>N/A</td>
<td>~ 6.5L +</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at randomization (median)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RRT Intervention</td>
<td>IHD only 47% (56% @ start)</td>
<td>CVVHDF 100% at start</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CRRT only 33% (44% @ start)</td>
<td>CRRT alone 71.4%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Combo 20%</td>
<td>Change to SLEDD alone 22.3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Change to IHD alone 1.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combo SLEDD/IHD 4.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>60 day mortality</td>
<td>90 day mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality – Early</td>
<td>48.5%</td>
<td>39.3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality – Delayed</td>
<td>49.7%**</td>
<td>54.7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% in Delayed arm that</td>
<td>51.0%</td>
<td>90.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>received RRT</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Ongoing RRT Initiation RCT: IDEAL-ICU study (France) – Initiated 2012

- Inclusion criteria (all must be present): → Adult, admission to an ICU
  - Patients in the **first 48 hrs of septic shock** developing AKI with at least one criterion characteristic of the **failure stage of the RIFLE classification** (= KDIGO stage 3)

- **“Early” RRT** is initiated immediately after the diagnosis of AKI (maximum of 12 hrs allowed between the diagnosis of AKI and initiation of RRT)

- **“Delayed” RRT** is initiated at least 48 hrs after the diagnosis of AKI; maximum margin of 12 hrs (i.e. up to 60 hrs) allowed before actual initiation

- **“Emergency” RRT** is initiated at discretion of clinician if at least one of the following criteria fulfilled:
  1) hyperkalemia (K+ ≥6.5 mEq/L) with characteristic electrocardiographic changes
  2) metabolic acidosis (pH <7.15) with base deficit > 5 mEq/L or bicarbonate < 18 mEq/L
  3) pulmonary edema
Ongoing RRT Initiation RCT: STARRT-AKI (Canada) – Enrolling

- **Inclusion criteria** (all must be present):
  - Adult, admission to an ICU + Serum creatinine ≥ 1.1 mg/dL women; ≥ 1.5 mg/dL men
  - **Severe AKI** defined by at least 2 of the following: 2-fold increase in serum creatinine during hospitalization or from pre-hospitalization baseline (KDIGO 2); oliguria (total urine output < 6 mL/kg over the preceding 12 hrs); Whole blood NGAL ≥ 400 ng/mL
  - Likelihood that an absolute indication for RRT will not arise in the subsequent 24 hours (K ≤ 5.5 mEq/L and bicarbonate ≥ 15 mEq/L)
  - CVP ≥ 8 mmHg

- **Standard RRT** is initiated if persistent AKI and one of the following:
  - K ≥ 6.0 mEq/L
  - Bicarbonate ≤ 10 mEq/L
  - Severe respiratory failure: PaO2/FiO2 < 200 and bilateral infiltrates
  - By 72 hrs after randomization, creatinine has not declined by more than 50%

- **Accelerated/pre-emptive RRT** is initiated as soon as possible and < 12 hours of eligibility
Acute Renal Support in the ICU

- **CRRT**
  - Cardiovascular instability (cardiogenic shock, septic shock, acute liver failure)
  - Volume control
  - Cerebral edema

- **IHD/PIRRT**
  - Hyperkalemia
  - Severe acidosis
  - Drug poisonings
  - Anticoagulation issues with CRRT

The Spectrum of RRT

- CRRT
- PIRRT
- Optimized IHD
- Conventional IHD
6 Steps For Successful CRRT

1. Close collaboration between CCM & nephrology

2. Goals of therapy
   - Daily discussion for volume removal & CRRT goals

3. Keep CRRT running – make ICU nurse happy
   - Establish & maintain a great vascular access
   - Anticoagulation options – use whenever possible

4. Address medication dosing daily

5. Ensure appropriate nutrition support

6. Avoid complications
   - Hypophosphatemia (avoid < 2.0)
Admitted to ICU. Aggressive volume resuscitation with 10L NS over the next 24 hrs
- BP improved to 105/58 but dependent low dose norepi @ 0.05 mcg/kg/min
- UOP only 120cc since admission

**Labs:**
- pH 7.22/48/88 with lactic acid 3.5 on 50% ventimask

Progressive resp distress secondary to worsening pulmonary infiltrates (ARDS), abd pain and distention requiring intubation
My “optimal” RST with CRRT

- **RRT as renal support therapy (RST)***
  - RST fills the gap between patients renal needs/demands & renal capability

- **Decide initial target/indication** for therapy
  - Volume
  - Acid/base control
  - Solutes, lytes

- **Early** initiation for **volume overload or acid/base control**
  - Volume overload associated with poor outcomes
  - Even small metabolic acid loads can necessitate augment mechanical ventilation to high pressures/volumes/rate → vent induced lung injury (VILI) → increased mortality

- **Establish great vascular access**

- **Dose at 25-30ml/kg/hr**
  - helps ensure at least 20ml/kg/hr including down-time

- **Anticoagulation whenever possible**
  - Citrate = great
  - As little as low-dose heparin @ 500 units/hr will help
Fluid Overload = > 10% increase in weight from baseline

OR for death if fluid overload present at RRT initiation = **2.07** (95% CI 1.27-3.37)
Volume Related Wt Gain at CRRT Initiation

Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study

Suvi T Vaara¹, Anna-Maija Korhonen¹, Kirs-Majka Kaukonen¹, Sara Nisula¹, Outi Inkinen², Sanna Hoppu³, Jouko J Laurila⁴, Leena Mildh⁵, Matti Reinikainen⁶, Vesa Lund⁷, Ilkka Parviainen⁷ and Ville Pettiloc⁸, for The FINNAKI study group

Vaara et al. Critical Care 2012, 16:R197
http://ccforum.com/content/16/5/R197

Figure 3 Ninety-day mortality according to the percentage of fluid accumulation prior to renal replacement therapy initiation

Comparison across groups P < 0.001
Section 5: Dialysis Interventions for Treatment of AKI

- **5.1.1**: Initiate RRT emergently when **life-threatening changes in fluid, electrolyte, and acid-base balance exist**. (Not Graded)

- **5.1.2**: Consider the **broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests**—rather than single BUN and creatinine thresholds alone—when making the decision to start RRT. (Not Graded)
My “optimal” CRRT

- Close attention to drug (especially antimicrobial) dosing
  - Sepsis is leading cause of death in AKI
  - Low antimicrobial levels unequivocally causes higher mortality in sepsis
  - Dose **aggressively** while on CRRT
    - est GFR (or CrCl) = therapy fluid flow rate (ml/hr) / 60

- **Remove volume** whenever hemodynamically acceptable
  - Volume overload is the **enemy** of overall patient & renal recovery
  - CRRT **more effective** for volume removal
    - Slow to transition to IRRT/IHD unless volume is **near/below admission weight**

- Optimize nutrition support during CRRT – **more later today**
  - Recommend daily protein intake of 1.5-2.5 g/kg/day while on CRRT
Future

- Encourage high-quality clinical research in CRRT & ICU-based RRT to define “optimal” therapy

- Encourage multi-centered clinical research comparing modality of therapies (CRRT, IRRT, PIRRT)
  - Using standardized, “optimal”, modern therapies ensuring proper medication dosing, nutrition therapy, etc.

- Evidence-based, patient-centered application of renal support therapies
Thank you!

Questions?

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Twitter: @criticalbeansmd