PW2 Workshop

AKI and Patient Selection for CRRT

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Albany Medical College,
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Patient Selection for RRT: Outline

• Who should get what: The patients
  • A brief description of AKI epidemiology
    • Increasing incidence
    • A problem of now and tomorrow: not just survival but also recovery

• The critically ill patient with AKI: Clinical targets
  • Uremia
  • Fluid overload
  • Electrolyte disorders: Dysnatremias
  • Acid base disorders

• Some should get RRT; others should NOT
  • How to decide who needs RRT

• When should we start: Timing
  • Timing definitions and timing-related outcomes

• CRRT in special circumstances
  • The brain; the liver; the heart; the kidney
Natural history of AKI-D

- **HOSPITAL ADMISSIONS**
  - 20% AKI
  - No RRT: 1–5 million/year
  - RRT: 1–2%
  - Survive: 40–60%
  - Recover: 70–90%
  - ESRD: Up to 80% develop CKD

- **Patient mix**
- **Co-morbidities**
- **Interventions**
- **Early recognition**
- **Management**
- **Modality RRT**
- **Timing RRT**
- **Fluid management**
- **Outpatient management**

HD, haemodialysis

**Natural history of AKI-D**

1. **No RRT**
   - 40–60% SURVIVE
   - 70–90% recover function
   - 10–50,000/year
   - 10–30% remain on HD
   - 40–80% ‘ESRD’

2. **RRT**
   - 20–60% die
   - Up to 80% develop CKD
   - 1–5 million/year

3. **HOSPITAL ADMISSIONS**
   - 20% AKI
   - 1–2% RRT

**SO, WHAT WORKS?**

- **Patient mix**
- **Co-morbidities**
- **Interventions**
- **Early recognition**
- **Management**

- **Modality RRT**
- **Timing RRT**
- **Fluid management**

- **Outpatient management**

HD, haemodialysis

Several well-done trials have been largely disappointing

- Antinflammatory and pleiotropic drugs (corticosteroids, statins, aspirin)
- Vasoactive or antiplatelet drugs to improve kidney perfusion (fenoldopam, clonidine, aspirin)
- Different fluid administration strategies (buffered crystalloid vs saline)
- Electronic health-record alerts for early stage AKI
- Ischemic pre-conditioning
# Options in Renal Replacement Therapy

<table>
<thead>
<tr>
<th>Operational Characteristic</th>
<th>Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Therapy</td>
<td>Intermittent, Extended or Continuous</td>
</tr>
<tr>
<td>Membrane Permeability</td>
<td>High-flux, Medium-flux</td>
</tr>
<tr>
<td>Treatment Technique</td>
<td>Diffusion (Dialysis), Convection (Hemoperfusion), both Hemadsorption Others</td>
</tr>
<tr>
<td>Equipment</td>
<td>Single-pass batch, Regular Hemodialysis or CRRT Machine</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>No A/C, Heparin or Citrate</td>
</tr>
</tbody>
</table>

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In AKI, RRT is a multidimensional task

The components

MACHINES
- MODALITY
  - Diffusion, Convection or both
- MEMBRANES/FILTERS
- SOLUTIONS
- BUFFERS
- PRESCRIBED DOSE
- MEASURED DOSE

ENVIRONMENT
- NURSING
- TECHS
- EDUCATION
- QUALITY MEASURES
- INSTITUTIONAL SUPPORT
- TEAM WORK

PATIENT
- MOF
- AKI
- COMORBIDITIES
- RENAL OR NON RENAL
- INDICATIONS
- FLUID STATUS
- HEMODYNAMICS
- ACID BASE
- DYSELECTROLYTEMIAS
- CATABOLISM
- DRUGS
- NUTRITION

OUTCOMES
- RECOVERY FUNCTION
- SURVIVAL
- HEMODYNAMIC STABILITY
- TIMING
- DELIVERED DOSE

Institutional Support
- Cost

Teamwork

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RRT Adequacy is Multidimensional

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RRT Adequacy is Multidimensional

- Urea based dose
- Timing
- Immuno homeostasis
- Anticoagulation
- Acid Base control
- Electrolyte control
- Drug removal
- Fluid balance
- Hemodynamic stability

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What are the characteristics of the “ideal” AKI RRT treatment in the ICU?

• Preserves homeostasis
• Does not increase co-morbidity
• Does not worsen patient’s underlying condition
• Is inexpensive
• Is simple to manage
• Is not burdensome for the ICU staff

N. Lameire et al, NDT 1999;14:2570-2573
Considerations in Renal Replacement Therapy for AKI

<table>
<thead>
<tr>
<th>Consideration</th>
<th>Components</th>
<th>Varieties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis Modality</td>
<td>Intermittent Hemodialysis</td>
<td>Daily, Every other day, SLED</td>
</tr>
<tr>
<td></td>
<td>Continuous renal replacement therapies</td>
<td>AV, VV</td>
</tr>
<tr>
<td></td>
<td>Peritoneal dialysis</td>
<td></td>
</tr>
<tr>
<td>Dialysis Biocompatibility</td>
<td>Membrane characteristics</td>
<td></td>
</tr>
<tr>
<td>Dialyzer Performance</td>
<td>Efficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flux</td>
<td></td>
</tr>
<tr>
<td>Dialysis Delivery</td>
<td>Timing of initiation</td>
<td>Early, Late</td>
</tr>
<tr>
<td></td>
<td>Intensity of dialysis</td>
<td>Prescription vs. Delivery</td>
</tr>
<tr>
<td></td>
<td>Adequacy of dialysis</td>
<td>Dialysis dose</td>
</tr>
</tbody>
</table>
MODALITIES OF CRRT

- **SCUF**
  - Blood In
  - UFC → Uf
  - \( Q_b = 100\, \text{ml/min} \quad Q_f = 2-8\, \text{ml/min} \)
  - Notes:

- **CVVH**
  - Blood In
  - UF → R → V
  - \( Q_b = 100-200\, \text{ml/min} \quad Q_f = 10-30\, \text{ml/min} \)
  - \( K = 15-45\, \text{L/h} \)

- **CVVHD**
  - Blood In
  - UF → R → V
  - \( Q_b = 100-200\, \text{ml/min} \quad Q_f = 2-4\, \text{ml/min} \)
  - \( K = 15-45\, \text{L/h} \)

- **CVVHDF**
  - Blood In
  - UF → D → V
  - \( Q_b = 100-200\, \text{ml/min} \quad Q_f = 10-30\, \text{ml/min} \)
  - \( Q_d = 10-30\, \text{ml/min} \quad K = 20-50\, \text{L/h} \)

- **CVVHDF-SLED**
  - Blood In
  - UF → D → V
  - \( Q_b = 100-200\, \text{ml/min} \quad Q_f = 2-8\, \text{ml/min} \)
  - \( Q_d = 50-200\, \text{ml/min} \quad K = 40-60\, \text{L/h} \)
  - Diffusion + Convection (Back Filtration)

- **CPF-PE**
  - Blood In
  - Plasmafilter
  - \( Q_b = 100-200\, \text{ml/min} \quad Q_f = 20-30\, \text{ml/min} \)
  - Can be coupled with CVVH or CVVHDF

- **CHP**
  - Blood In
  - Adsorbent
  - \( Q_b = 100-200\, \text{ml/min} \)
  - Can be coupled with CVVH or CVVHDF

- **CPFA**
  - Blood In
  - Plasma → Adsorbent → Uf
  - \( Q_b = 100-200\, \text{ml/min} \quad Q_f = 20-30\, \text{ml/min} \)
  - Can be coupled with CVVH or CVVHDF

- **HVHF**
  - Blood In
  - UF → R → V
  - \( Q_b = 200-300\, \text{ml/min} \quad Q_f = 50-100\, \text{ml/min} \)
  - \( K = 60-120\, \text{L/h} \)
## How Do We Choose a Specific RRT Modality?

<table>
<thead>
<tr>
<th>Therapeutic Goal</th>
<th>Hemodynamics</th>
<th>Preferred Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid Removal</td>
<td>Stable</td>
<td>Intermittent Isolated UF</td>
</tr>
<tr>
<td></td>
<td>Unstable</td>
<td>Slow Continuous UF</td>
</tr>
<tr>
<td>Urea Clearance</td>
<td>Stable</td>
<td>Intermittent Hemodialysis</td>
</tr>
<tr>
<td></td>
<td>Unstable</td>
<td>CRRT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Convection: CAVH, CVVH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diffusion: CAVHD, CVVHD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Both: CAVHDF, CVVHDF</td>
</tr>
<tr>
<td>Severe Hyperkalemia</td>
<td>Stable/Unstable</td>
<td>Intermittent Hemodialysis</td>
</tr>
<tr>
<td>Severe Metabolic Acidosis</td>
<td>Stable</td>
<td>CRRT</td>
</tr>
<tr>
<td></td>
<td>Unstable</td>
<td></td>
</tr>
<tr>
<td>Severe Hyperphosphoremia</td>
<td>Stable/Unstable</td>
<td>CRRT</td>
</tr>
<tr>
<td>Brain Edema</td>
<td>Unstable</td>
<td>CRRT</td>
</tr>
</tbody>
</table>

*Cerdá and Ronco Semin Dialysis 2008*
CRRT Machines

NexStage

B.Braun

Fresenius

Prismaflex
CRRT Modalities


FLUID OVERLOAD SHOULD BE AVOIDED
Oliguria is associated with worse mortality

* $p < 0.001$  **$p = 0.013$
Greater Cumulative Fluid Balance is Associated with Worse Mortality

* p < 0.001 ** p = 0.064

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BEDSIDE Registry
Cumulative Fluid Balance in Septic Shock-Induced Acute Lung Injury is Greater in Liberal Fluid Management

ARDS Clinical Trial Network, NEJM 2006
Fluid Accumulation in the FACTT Trial

ARDS Clinical Trial Network, NEJM 2006

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Being Stingy with Fluid Strategies in Acute Lung Injury Will Not Worsen Renal Outcomes

MORE CARDIOVASCULAR AND CNS COMPLICATIONS IN THE LIBERAL STRATEGY GROUP

Table 3. Main Outcome Variables.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Conservative Strategy</th>
<th>Liberal Strategy</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death at 60 days (%)</td>
<td>25.5</td>
<td>28.4</td>
<td>0.30</td>
</tr>
<tr>
<td>Ventilator-free days from day 1 to day 28†</td>
<td>14.6±0.5</td>
<td>12.1±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU-free days‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days 1 to 7</td>
<td>0.9±0.1</td>
<td>0.6±0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days 1 to 28</td>
<td>13.4±0.4</td>
<td>11.2±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Organ-failure-free days†‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days 1 to 7</td>
<td>Cardiovascular failure</td>
<td>3.9±0.1</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>CNS failure</td>
<td>3.4±0.2</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
<td>5.5±0.1</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>Hepatic failure</td>
<td>5.7±0.1</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>Coagulation abnormalities</td>
<td>5.6±0.1</td>
<td>0.23</td>
</tr>
<tr>
<td>Days 1 to 28</td>
<td>Cardiovascular failure</td>
<td>19.0±0.5</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>CNS failure</td>
<td>18.8±0.5</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
<td>21.5±0.5</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>Hepatic failure</td>
<td>22.0±0.4</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>Coagulation abnormalities</td>
<td>22.0±0.4</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Dialysis to day 60

| Patients (%) | 10 | 14 | 0.06 |
| Days         | 11.0±1.7 | 10.9±1.4 | 0.96 |
Positive fluid balance is an independent predictor of mortality in AKI

Table 3. Relative odds of death by FACTT study day 60 associated with average daily fluid balance and furosemide dose following AKI

<table>
<thead>
<tr>
<th>Adjustment</th>
<th>Fluid Balance (Post-AKI, in Mean L/Day)</th>
<th></th>
<th>Furosemide Dose (Post-AKI, in Mean 100 mg/Day)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>None (univariate)</td>
<td>1.73 (1.47 to 2.03)</td>
<td>&lt;0.001</td>
<td>0.38 (0.23 to 0.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Full model</td>
<td>1.61 (1.29 to 2.00)</td>
<td>&lt;0.001</td>
<td>0.54 (0.31 to 0.94)</td>
<td>0.028</td>
</tr>
<tr>
<td>+ Post-AKI fluid balance</td>
<td>1.56 (1.25 to 1.95)</td>
<td>&lt;0.001</td>
<td>0.73 (0.42 to 1.26)</td>
<td>0.255</td>
</tr>
<tr>
<td>+ Post-AKI furosemide dose</td>
<td>1.61 (1.32 to 1.96)</td>
<td>&lt;0.001</td>
<td>0.48 (0.28 to 0.81)</td>
<td>0.007</td>
</tr>
<tr>
<td>Final model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Grams ME et al
CJASN 2011,6:966-73
Fluid Overload Is Associated with Worse Survival

Bouchard et al
KI 2009;76:422-27
Fluid Overload and Survival: Dose-Response Relationship?

Bouchard et al  
KI 2009;76:422-27  

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Fluid Overload and Survival: Longer Duration is Associated with Worse Mortality

Bouchard et al
KI 2009;76:422-27

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Fluid Overload is Associated with Delayed Functional Recovery

Heung et al, NDT 2012

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CRRT Allows Better Fluid Management

**Figure 4:** Effect of Dialysis Modality on Fluid Balance

- **Bouchard et al.** *KI* 2009;76:422-27
Fluid Balance is Best Achieved with CRRT

Augustine et al, AJKD 2004

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Hemodynamic Stability: CRRT vs IHD

Augustine et al, AJKD 2004

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So then, why is CRRT associated with *better* hemodynamic stability?

- **Maintenance of intravascular compartment volume**
  - Prolonged treatments permit lower fluid removal rates
    - IHD: 3 L in 3 hours = 1 L/h UF rate
    - CRRT: 3 L in 24 hrs = 0.125 ml/h UF rate
  - Urea diffusion is faster with IHD than CRRT
    - IHD: Urea clearance ~160 ml/min
    - CRRT: Urea clearance ~15-30 ml/min

- **Convective sodium removal rate** [hemofiltration/hemodiafiltration] is less than diffusive removal rate [hemodialysis]

- **Decreased core temperature**

- **Convective removal of inflammatory mediators could contribute to hemodynamic stability**
DECREASED CAPILLARY REFILLING AND LOSS OF WATER TO INTERSTITIUM

DECREASED I/VASCULAR VOLUME

INTRACELLULAR EDEMA

ULTRAFILTRATION

DIALYSIS
Loss of osmotically active solutes (urea)

Systemic Capillary

\[ [\text{Na}^+]_p \text{ water higher than } [\text{Na}^+]_d \text{ dialysate (can be changed)} \]

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H2O

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Higher plasma oncotic pressure facilitates capillary refilling.

Little change in I/Vascular volume.

Replacement fluid: Isotonic [Na+] 150 mEq/L.

Hemofiltration: Small solute concentrations equal to plasma (No transcapillary osmotic pressure gradient).

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TIMING OF INITIATION OF RRT
TIMING OF INITIATION OF RRT

• What is timing??

• What is early and what is late?

• How many “late” patients were dialyzed?

• Uncertain

• Lab cutoff values (urea, Cr)

• Urine output measurements

• Time from ICU admission

• KDIGO stage

• Severity of disease scores

• Composite criteria

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Timing: Study Design

- **MEETS RRT CRITERIA**
  - **RANDOMIZATION**
    - **EARLY**
      - DIES
      - RECOVERS
      - DOESN’T RECOVER
    - **LATE**
      - DIES
      - RECOVERS
      - NEVER DIALYZED
      - RECEIVES RRT

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Predicting likely outcomes from a study of accelerated RRT in AKI is complex.

Prowle, Davenport KI 2015;88:670

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### Most Recent RCT Timing Studies

<table>
<thead>
<tr>
<th>STUDY</th>
<th>CRITERIA</th>
<th>RRT MODALITY</th>
<th>INCIDENCE OF RRT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>EARLY</strong></td>
<td><strong>LATE</strong></td>
<td><strong>EARLY</strong></td>
</tr>
<tr>
<td>Bouman CCM 2002</td>
<td>RRT within 12 h post inclusion</td>
<td>Urea&gt;40 mM, K&gt;6.5 mEq/L, severe pulmonary edema</td>
<td>CVVH</td>
</tr>
<tr>
<td>Sugahara HD Int 2004</td>
<td>U.O&lt;30 ml/min 3 h or daily UO &lt;750 ml</td>
<td>U.O.&lt;20 ml/h 2 conseq hours or daily UO&lt;500 ml</td>
<td>CVVHD</td>
</tr>
<tr>
<td>Jamale AJKD 2013</td>
<td>BUN&gt;70 mg/dl+/-Cr&gt;7 mg/dl</td>
<td>Refractory K, fluid OL, acidosis malnutrition</td>
<td>IHD</td>
</tr>
<tr>
<td>Wald KI 2015</td>
<td>RRT within 12 h eligibility</td>
<td>K&gt;6 mEq/L; HCO3&lt;10 mM; resp failure, persistent AKI</td>
<td>IHD, SLED, CRRT</td>
</tr>
<tr>
<td>Gaudry AKIKI NEJM 2016</td>
<td><strong>RRT within 6 h of reaching AKI 3</strong></td>
<td>Severe K, uremia, Mtb acidosis, pulm edema, oliguria 72 h post randomization</td>
<td>IHD, CRRT</td>
</tr>
<tr>
<td>Zarbock ELAIN JAMA 2016</td>
<td>Early RRT at AKI 2 within 8 hours</td>
<td>BUN&gt;100 mg/dl; K&gt;6 mEq/L; Mg&gt;8 mEq/L; UO&lt;200 ml/12 h, edema, <strong>RRT within 12 h of reaching AKI 3</strong></td>
<td>CVVHDF</td>
</tr>
</tbody>
</table>
Dialysis vs. Non-Dialysis in AKI: A Propensity-Matched Cohort Study

Wilson FP et al CJASN 2014;9:673
N=6119; 602 received RRT

Figure 1. Kaplan–Meier survival curves of dialyzed and nondialyzed patients in the (A) full and (B) matched cohorts. Time 0 is the onset of AKI in the full cohort and the day of initiation of dialysis (or match day) in the matched cohort.

LONGEST DELAY

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Mr Elain, a 65 year old critically ill male is admitted to the ICU with the following findings ...

- Urine output 445 ml/day (0.5 ml/Kg/h)
- Serum Creatinine 1.9 mg/dl
- BUN 38.5 mg/dl
- Potassium 5.1 mEq/L
- Bicarbonate 20.9 mEq/L
- Hgb 8.6 g/dl
- WBC 16.000 /μL
- SOFA 15.6 (HIGH)
- On Vent
- On Pressors
- CUMM FLUID BALANCE +6.8 L

KIDGO 2

OPTIONS:

- YOU DECIDE TO DIALYZE IMMEDIATELY
- YOU DECIDE TO WAIT 24 HOURS
Timing:
ELAIN Study Design

MEETS RRT CRITERIA

RANDOMIZATION

112/112
EARLY

DIES
RECOVERS
DOESN'T RECOVER

108/119
LATE

DIES
RECOVERS
DOESN'T RECOVER

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ELAIN: Early vs Late Initiation of RRT in Critically Ill Patients with AKI

Average time difference between “early” and “late” was <24 hours.
Table 2. Patient Characteristics at the Time of Renal Replacement Therapy (RRT) Initiation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early (n = 112)</th>
<th>Delayed (n = 119)</th>
<th>Absolute Difference (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>.36</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>&lt;.001</td>
</tr>
<tr>
<td>Time from KDIGO 2 to RRT, median (Q1, Q3), h</td>
<td>5.4 (2.2)</td>
<td>50.4 (45.4, 55.4)</td>
<td>-34.5 (−45.0 to −24.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Serum creatinine, mean (SD), mg/dL</td>
<td>1.9 (0.6)</td>
<td>2.4 (1.0)</td>
<td>-0.5 (−0.7 to −0.3)</td>
<td>.001</td>
</tr>
<tr>
<td>Blood urea nitrogen, mean (SD), mg/dL</td>
<td>38.5 (15.5)</td>
<td>47.5 (21.6)</td>
<td>-9.0 (−14.1 to −3.9)</td>
<td>.001</td>
</tr>
<tr>
<td>Potassium, mean (SD), mEq/L</td>
<td>5.1 (0.9)</td>
<td>5.1 (0.9)</td>
<td>0.0 (−0.1 to 0.3)</td>
<td>.69</td>
</tr>
<tr>
<td>Bicarbonate, mean (SD), mEq/L</td>
<td>20.9 (3.6)</td>
<td>20.7 (3.7)</td>
<td>0.1 (−0.9 to 1.1)</td>
<td>.74</td>
</tr>
<tr>
<td>Hemoglobin, mean (SD), g/dL</td>
<td>8.6 (1.3)</td>
<td>8.6 (1.4)</td>
<td>0.0 (−0.3 to 0.3)</td>
<td>.23</td>
</tr>
<tr>
<td>White blood cells, mean (SD), ×10⁹/L</td>
<td>16.2 (9.8)</td>
<td>16.5 (9.5)</td>
<td>-0.3 (−2.8 to 2.3)</td>
<td>.93</td>
</tr>
</tbody>
</table>

Zarbock JAMA 2016;315(20):2190-2199

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Mr Akiki, a 65 year old critically ill male is admitted to the ICU with the following findings...

- Urine output 250 ml/day (0.2 ml/Kg/h)
- Serum Creatinine 3.25 mg/dl
- BUN 53 mg/dl
- Potassium 4.4 mEq/L
- Bicarbonate 18 mEq/L
- Hgb 8.6 g/dl
- WBC 16,000 /μL
- SOFA 10.9 (MID-HIGH)
- On Vent
- On Pressors

KIDGO 3

OPTIONS:

- YOU DECIDE TO DIALYZE WITHIN 2 HOURS
- YOU DECIDE TO WAIT 54 HOURS
Timing: Study Design

DIALYSIS OR NO DIALYSIS

MEETS RRT CRITERIA

RANDOMIZATION

98%

EARLY

DIES

RECOVERS

DOESN'T RECOVER

LATE

DIES

RECOVERS

NEVER DIALYZED

RECEIVES RRT

51%

49%

DIES

RECOVERS

DOESN'T RECOVER

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Timing: Study Design

MORTALITY

MEETS RRT CRITERIA

RANDOMIZATION

EARLY

48 %

MORE CATHETER RELATED INFECTIONS

DIES
RECOVERS
DOESN’T RECOVER

LATE

61.8 %

RECEIVES RRT

NEVER DIALYZED

37 %

DIES
RECOVERS

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Initiation Strategies RRT
AKI in the ICU

AKIKI

Artificial Kidney Initiation in Kidney Injury Study Group

Figure 1. Probability of Survival and Timing of Renal-Replacement Therapy.

Figure 2. Probability of Adequate Urine Output without the Need for Renal-Replacement Therapy.

Shown are the Kaplan–Meier curves of the probability of a patient having urine output, for at least 1 day, of more than 1000 ml per 24 hours in the
SYSTEMATIC REVIEW & META-ANALYSIS OF RECENT RANDOMIZED CONTROLLED TRIALS

EARLY INITIATION ON MORTALITY

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Weight(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouman, 2002</td>
<td>1.26 (0.59, 2.95)</td>
<td>10.90</td>
</tr>
<tr>
<td>Sugahara, 2004</td>
<td>0.17 (0.05, 0.81)</td>
<td>4.87</td>
</tr>
<tr>
<td>Jamale, 2013</td>
<td>1.88 (0.89, 3.17)</td>
<td>13.35</td>
</tr>
<tr>
<td>Wahl, 2015</td>
<td>1.03 (0.62, 1.71)</td>
<td>16.78</td>
</tr>
<tr>
<td>Gaudry, 2016</td>
<td>0.97 (0.83, 1.14)</td>
<td>29.30</td>
</tr>
<tr>
<td>Zarbock, 2018</td>
<td>0.72 (0.54, 0.95)</td>
<td>25.03</td>
</tr>
<tr>
<td>Overall</td>
<td>0.93 (0.68, 1.28)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

EARLY INITIATION ON RECOVERY

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Weight(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bozman, 2002</td>
<td>3.08 (1.13, 7.32)</td>
<td>3.19</td>
</tr>
<tr>
<td>Sugahara, 2004</td>
<td>5.00 (0.28, 95.61)</td>
<td>4.26</td>
</tr>
<tr>
<td>Jamale, 2013</td>
<td>1.04 (0.31, 3.49)</td>
<td>25.29</td>
</tr>
<tr>
<td>Wahl, 2015</td>
<td>0.22 (0.01, 4.59)</td>
<td>4.00</td>
</tr>
<tr>
<td>Gaudry, 2016</td>
<td>0.37 (0.10, 1.39)</td>
<td>21.31</td>
</tr>
<tr>
<td>Zarbock, 2018</td>
<td>1.06 (0.41, 2.73)</td>
<td>41.39</td>
</tr>
<tr>
<td>Overall</td>
<td>0.88 (0.48, 1.62)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

EARLY INITIATION ON COMPOSITE DEATH OR HD

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Weight(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouman, 2002</td>
<td>1.37 (0.66, 2.84)</td>
<td>8.82</td>
</tr>
<tr>
<td>Sugahara, 2004</td>
<td>0.33 (0.14, 0.78)</td>
<td>5.88</td>
</tr>
<tr>
<td>Jamale, 2013</td>
<td>1.50 (0.88, 2.57)</td>
<td>13.38</td>
</tr>
<tr>
<td>Wahl, 2015</td>
<td>0.93 (0.57, 1.52)</td>
<td>14.78</td>
</tr>
<tr>
<td>Gaudry, 2016</td>
<td>0.94 (0.81, 1.10)</td>
<td>30.29</td>
</tr>
<tr>
<td>Zarbock, 2018</td>
<td>0.75 (0.59, 0.97)</td>
<td>25.85</td>
</tr>
<tr>
<td>Overall</td>
<td>0.91 (0.71, 1.17)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Xu et al Clin Exp Nephrol 2016

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Ongoing timing trials... Stay tuned!


AKI INDUCES DISTANT ORGAN EFFECTS

Scheel et al KI 2008
RRT in Special Circumstances

• Patients with an increased risk of bleeding
• Hemodynamically unstable patients
• Patients with or at risk of cerebral edema
• Dysnatremias
• Severe acidosis and lactic acidosis
RRT in Special Circumstances

- Patients with an increased risk of bleeding
  - No anticoagulation
  - Citrate anticoagulation
  - HIT type II: Argatroban

- Hemodynamically unstable patients

- Patients with or at risk of cerebral edema

- Dysnatremias

- Severe acidosis and lactic acidosis
RRT in Special Circumstances

- Patients with an increased risk of bleeding
  - No anticoagulation
  - Citrate anticoagulation
  - HIT: Argatroban
- Hemodynamically unstable patients
  - Continuous techniques: CVVH, CVVHD, CVVHDF
- Patients with or at risk of cerebral edema
- Dysnatremias
- Severe acidosis and lactic acidosis
Now, What About Renal Replacement Therapy and the *Brain*?
Follow-up Head CT 14 days of IHD

Figure 1  Brain CT and physiologic data of the patient

A

B

C

D

Ko et al Neurology 2012;78:e36

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RRT IS CRITICAL IN CERTAIN SITUATIONS...

- Patients with intra cranial hypertension or cerebral edema
  - Autoregulation is lost!
  - Sudden changes in systemic or intra-abdominal pressure change intracranial pressure
    - Patients with abdominal compartment syndrome
    - Patients with fulminant liver failure or acute decompensated liver cirrhosis

- Patients with severe azotemia
  - Correct azotemia *slowly*, to avoid dialysis dysequilibrium and worsened brain edema

- Patients with hyponatremia
  - Correct [Na]p *very slowly* to avoid osmotic demyelination syndrome
  - Urea protects against osmotic demyelination syndrome
Changes in Intracranial Pressure during Haemofiltration in Oliguric Patients with Grade IV Hepatic Encephalopathy

HF: Gambro Qb 200-250
Isovolemic 17 L exchanges 3.5-4 hrs.

CAVHF: 400-1000 ml/h 24-160 hrs.

Davenport A et al Nephron 1989;53:142-146
Brain density changes during renal replacement in critically ill patients with ARF
Continuous HF vs. IHD

Acute fulminant liver failure or acute-on-chronic liver failure

- Hepatic encephalopathy is in part determined by brain edema, so avoid brain swelling

- Hyponatremia is a common complication, which commonly causes brain edema

- And low blood urea concentration increases risk of ODS; high urea protects from ODS

- Low efficiency, highly flexible CRRT is preferable
The Brain in AKI
In AKI, increased water permeability and water contents increase risk of brain edema.

Liu et al JASN 2008

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RRT in Special Circumstances

• Patients with an increased risk of bleeding
  • No anticoagulation
  • Citrate anticoagulation
  • HIT: Argatroban

• Hemodynamically unstable patients
  • Continuous techniques: CVVH, CVVHD, CVVHDF

• Patients with or at risk of cerebral edema
  • Continuous techniques: CVVH, CVVHD, CVVHDF

• Dysnatremias; Risk of Osmotic Demyelination Syndrome
  • Extended or Continuous RRT

• Severe acidosis and lactic acidosis
A High BUN May Protect Against Osmotic Demyelination

Increased ICEL water contents protects from sudden cell shrinking induced by rapid Na⁺ correction.

**NEURONS**

**BLOOD-BRAIN BARRIER**

**DURING DIALYSIS**

**DIALYZER**

**DIALYSIS**

**UREA**

**STIMULATED IDIOSMOL RE-UPTAKE**

Water moves intracellularly

Plasma Urea decreases rapidly

Intracellular Urea decreases slowly

Soupart A Brain Res 2000;852:167
Oo TN Semin Dial 2003;16:68
Soupart A JASN 2002;13:1433

Dr Cerda AKI&CRRT 2017
RRT in Special Circumstances

• PATIENTS WITH LIVER FAILURE
  
  • Hyponatremia, ascites and hypotension
    • Compartment syndrome and hypotension worsen brain edema
  
  • Fulminant liver failure and Hepatic Encephalopathy
    • Brain edema
    • Role of hyponatremia in worsening brain edema
    • Low urea concentration worsens chances of Osmotic Demyelination Syndrome
  
  • Coagulopathy
    • Decreased or increased coagulation?

Stravitz RT CCM 2007;35:2498
Davenport A Contr Nephrol 2007;156:259
Davenport A Hemodial Int 2008;12:307
Dr Cerda AKI&CRRT 2017
RRT in Special Circumstances

- Patients with an increased risk of bleeding
  - No anticoagulation
  - Citrate anticoagulation
  - HIT: Argatroban

- Hemodynamically unstable patients
  - Continuous techniques: CVVH, CVVHD, CVVHDF

- Patients with or at risk of cerebral edema
  - Continuous techniques: CVVH, CVVHD, CVVHDF

- Dysnatremias; Risk of Osmotic Demyelination Syndrome
  - Extended or Continuous RRT

- Severe acidosis and lactic acidosis
  - Hemodynamically stable: Hemodialysis
  - Hemodynamically unstable or Lactic Acidosis: CRRT
The components