Timing, Dosing and Selecting of modality of RRT for AKI - the ERBP position statement

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When to initiate acute dialysis?

Generally accepted indications

- Refractory hyperkalaemia (>6.5 mmol/l)
- Refractory volume overload
- Refractory metabolic acidosis (pH ≤ 7.1)
- Uraemic organ complications (e.g. pericarditis)

‘Timely’ start:
- Serum urea concentration?
- Serum creatinine?
- AKI Stage?
- ????
Timing of Renal Replacement Therapy Initiation in Acute Renal Failure: A Meta-analysis

Victor F. Seabra, MD,1 Ethan M. Balk, MD, MPH,2 Orfeas Liangos, MD,3 Marie Anne Sosa, MD,3 Miguel Cendoroglo, MD,4 and Bertrand L. Jaber, MD, MS3

A. Jörres 10-2015

Seabra et al., AJKD 2008; 52: 272-84

Most studies favour „early“ start of RRT

“Paucity of randomized controlled trials, use of variable definitions of early RRT, and publication bias preclude definitive conclusions”
AKI Guideline

- Initiate RRT emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist that cannot be managed by conservative treatment. (Not Graded)

1. 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)

Jörres A et al., NDT 2013; 28: 2940-5
Practical Approach

• Acute RRT should be initiated once AKI is established but before overt complications have developed.

• The decision to start RRT should remain a clinical decision based on fluid, electrolyte and metabolic status of each individual patient.

• The threshold for initiating RRT should be lowered when AKI occurs as part of multi-organ failure.

• The initiation of RRT may be deferred if the underlying clinical condition is improving and there are early signs of renal recovery (e.g., increase in urine output).
Scenario #1
Isolated AKI (e.g., pre-renal; radiocontrast-induced…)

- Check for acute RRT indications
- Restore fluid status, correct electrolyte abnormalities
- Treat underlying problems
- Re-evaluate RRT indications regularly (at least daily)

- Observe trends of laboratory values; consider RRT if oliguria persists and/or creatinine/urea continue to rise over several days
Scenario #2
AKI as part of MODS (e.g., sepsis; shock; ...)

• Check for acute RRT indications
• Restore fluid status and circulation, correct electrolyte abnormalities
• Treat underlying problems

• If oliguria persists despite adequate fluid resuscitation and hemodynamic management, consider to start RRT without further delay (i.e. within 12-24 hours)
ARRT: „Biochemical“ Indications

- **Refractory** hyper-/hyponatraemia or hypercalcaemia
- Tumour lysis syndrome (uric acid ↑↑, phosphate ↑↑)
- Severe lactic acidosis

**Temporary** Bridging

- Underlying problem solvable
- Bridging to causal therapy:
  - Ventricular assist system
  - Surgical treatment
  - Treatment of infections
AKI in the ICU

CRRT
or
IHD

?
Fluid balance during RRT

UF / Time $\uparrow$

Hypotension
Organ perfusion $\downarrow$
Continuous or intermittent treatment?

- CRRT
- Daily IHD

Fluid removal over time (days): Monday, Tuesday, Wednesday, Thursday, Friday.
Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: A meta-analysis

Sean M. Bagshaw, MD, MSc; Luc R. Berthiaume, MD; Anthony Delaney, MBBS, MSc; Rinaldo Bellomo, MD

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratio (95% CI)</th>
<th>CRRT No. of events</th>
<th>IRRT No. of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>simpson (1993)</td>
<td>0.50 (0.21, 1.20)</td>
<td>46/65</td>
<td>32/38</td>
</tr>
<tr>
<td>kierdorf (1994)</td>
<td>0.81 (0.36, 1.82)</td>
<td>105/121</td>
<td>82/90</td>
</tr>
<tr>
<td>john (2001)</td>
<td>1.00 (0.15, 6.78)</td>
<td>54/84</td>
<td>40/82</td>
</tr>
<tr>
<td>mehta (2001)</td>
<td>0.94 (0.34, 2.78)</td>
<td>37/52</td>
<td>31/52</td>
</tr>
<tr>
<td>gasparovic (2003)</td>
<td>0.89 (0.35, 2.29)</td>
<td>27/40</td>
<td>28/40</td>
</tr>
<tr>
<td>augustine (2004)</td>
<td>0.91 (0.45, 1.85)</td>
<td>34/70</td>
<td>28/55</td>
</tr>
<tr>
<td>uehlinger (2005)</td>
<td>0.95 (0.61, 1.48)</td>
<td>118/175</td>
<td>126/184</td>
</tr>
<tr>
<td>vinsonneau (2006)</td>
<td>0.83 (0.53, 1.31)</td>
<td>100/172</td>
<td>90/144</td>
</tr>
<tr>
<td>lins (unpub)</td>
<td>0.99 (0.78, 1.26)</td>
<td>459/726</td>
<td>432/677</td>
</tr>
</tbody>
</table>

No survival benefit with CRRT vs. iHD
The effect of continuous versus intermittent renal replacement therapy on the outcome of critically ill patients with acute renal failure (CONVINT): a prospective randomized controlled trial

Joerg C Schefold1, Stephan von Haehling2, Rene Pschowski1,2, Thorsten Onno Bender2, Cathrin Berkmann2, Sophie Briegel1, Dietrich Hasper1 and Achim Jörres1

Prospective randomized clinical trial, 250 critically ill patients with AKI

Prospective randomized clinical trial, 250 critically ill patients with AKI

No difference regarding patient survival, duration of ARRT, or renal recovery between patients treated initially with IHD vs. CVVH

<table>
<thead>
<tr>
<th>Variable</th>
<th>IHD (n=128)</th>
<th>CVVH (n=122)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival at 14 days post RRT</td>
<td>39.5%</td>
<td>43.9%</td>
<td>0.81</td>
</tr>
<tr>
<td>30-day mortality rate</td>
<td>52.4%</td>
<td>45.4%</td>
<td>0.60</td>
</tr>
<tr>
<td>Hospital mortality rate</td>
<td>60.3%</td>
<td>54.6%</td>
<td>0.72</td>
</tr>
<tr>
<td>Days in ICU</td>
<td>25.2±40.1</td>
<td>22.3±26.1</td>
<td>0.50</td>
</tr>
<tr>
<td>Days in hospital</td>
<td>33.9±49.3</td>
<td>32.4±37.4</td>
<td>0.79</td>
</tr>
<tr>
<td>Days on RRT</td>
<td>17.2±37.1</td>
<td>13.7±17.9</td>
<td>0.35</td>
</tr>
<tr>
<td>RRT modality switch</td>
<td>25 (19.5%)</td>
<td>56 (45.9%)</td>
<td>0.002</td>
</tr>
<tr>
<td>RRT dependency @ day 21</td>
<td>20 (32.3%)</td>
<td>20 (29.9%)</td>
<td>0.97</td>
</tr>
<tr>
<td>RRT dependency @ day 60</td>
<td>14 (26.4%)</td>
<td>13 (22.8%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Days on vasopressors</td>
<td>4.3±3.7</td>
<td>4.5±3.7</td>
<td>0.75</td>
</tr>
<tr>
<td>Days on mechanical ventilation</td>
<td>8.1±8.8</td>
<td>7.2±6.5</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Mantel-Haenszel logrank p-value 0.358
HR 0.85 (95% CI 0.59-1.21)
Chi square 0.844

n=250

Study days following randomisation

Survival probability (%)
The Association Between Renal Replacement Therapy Modality and Long-Term Outcomes Among Critically Ill Adults With Acute Kidney Injury: A Retrospective Cohort Study*

- Critically ill adults who initiated dialysis for AKI between July 1996 and December 2009 and who survived to at least 90 days after ARRT initiation.

- 2,004 patients receiving CRRT matched to 2,004 patients receiving IHD; median follow-up 3 years.

- The risk of chronic dialysis was significantly lower among patients who initially received CRRT versus IHD (hazard ratio, 0.75; 95% CI, 0.65–0.87).

- This relation was more prominent among those with preexisting chronic kidney disease

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**Figure 2.** Cumulative risk of chronic dialysis among critically ill patients with acute kidney injury surviving to day 90 after commencement of renal replacement therapy who were initially treated with continuous renal replacement therapy (CRRT) (dashed line) versus intermittent hemodialysis (IHD) (solid line).
Extended Dialysis (SLED, PIRRT)
Fundamental principles

- Use of a modified or standard dialysis machine
- Use of diffusion, convection or any combination of the two
- Application of a decreased intensity of solute removal compared with IHD
- Extended duration of treatment beyond the typical 3 or 4 hr of standard IHD (hence the term prolonged) but not beyond an 8-12 hr period (hence the term intermittent)
- Use of "on-line" generation of dialysate or replacement fluid from tap water

Bellomo, Crit Care Resusc. 2002; 4: 281-90
Sustained low efficiency dialysis using a single-pass batch system in acute kidney injury - a randomized interventional trial: the REnal Replacement Therapy Study in Intensive Care Unit PatiEnts

- Prospective RCT in 232 surgical AKI patients comparing 12-h SLED-BD or to 24-h predilutional CVVH

- **Similar 90-day mortality** (SLED: 49.6% vs. CVVH: 55.6%, P = 0.43) and haemodynamic stability, but SLED-BD group had
  - significantly fewer days of mechanical ventilation (17.7±19.4 vs. 20.9±19.8, P=0.047)
  - fewer days in the ICU (19.6 ± 20.1 vs. 23.7 ± 21.9, P = 0.04)
  - needed fewer blood transfusions (1,375 ± 2,573 ml vs. 1,976 ± 3,316 ml, P = 0.02)

- **With SLED-BD substantial reduction in nursing time spent for renal replacement therapy** (P < 0.001) resulting in lower costs.
Clinical Choice of RRT Modalities

| Table 7.12.1 Potential advantages (+) and disadvantages (−) of CRRT, SLED, and IHD |
|---------------------------------|------|------|------|
|                                 | CRRT | SLED | IHD  |
| Hemodynamic tolerance           | ++   | ++   | −    |
| Control of hyperhydration       | ++   | ++   | −    |
| Low risk for dysequilibrium or cerebral edema | ++ | ++ | − |
| Emergency correction of hyperkalemia | −   | −    | ++  |
| Anticoagulation required        | −    | −    | +    |
| Platelet loss/activation        | −    | −    | +    |
| Effect on hyperpyrexia          | +    | +    | −    |
| Patient mobility                | −    | +    | ++   |
| Time for interventions          | −    | +    | ++   |
| Antibiotic dosing               | −    | −    | +    |
| Loss of nutrients, trace elements, electrolytes | − | + | + |
| Material costs                  | −    | ++   | ++   |

CRRT continuous renal replacement therapy, IHD intermittent hemodialysis, SLED sustained low-efficiency dialysis

Acute PD: Advantages

- No systemic anticoagulation required
- Hemodynamic stability
  - No extracorporeal circulation
  - Slower fluid removal
  - Slower solute removal
  - Less risk for dysequilibrium
- Better (faster) renal recovery (?)
- Easy to use
  - No hardware required
  - No electricity required
Acute PD: Disadvantages

• Limited clearance
• Slower correction of electrolyte disorders
• Slower/limited ultrafiltration
• May impede respiration (ventilated patients)
• (Risk of hyperglycemia)
• (Risk of infection)
Use of Peritoneal Dialysis in AKI: A Systematic Review

Chang Yin Chionh, Sachin S. Soni, Fredric O. Finkelstein, Claudio Ronco, and Dinna N. Cruz

A. Cohort Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>PD Events</th>
<th>PD Total</th>
<th>EBP Events</th>
<th>EBP Total</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hadidy 1989</td>
<td>0</td>
<td>4</td>
<td>25</td>
<td>77</td>
<td>0.23 [0.01, 4.41]</td>
</tr>
<tr>
<td>Chow 2007 (A)</td>
<td>8</td>
<td>12</td>
<td>2</td>
<td>3</td>
<td>1.00 [0.07, 14.64]</td>
</tr>
<tr>
<td>Kumar 1990</td>
<td>25</td>
<td>42</td>
<td>2</td>
<td>3</td>
<td>0.74 [0.06, 8.77]</td>
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<tr>
<td>Chow 2007 (B)</td>
<td>12</td>
<td>26</td>
<td>3</td>
<td>4</td>
<td>0.29 [0.03, 3.12]</td>
</tr>
<tr>
<td>Werb 1979</td>
<td>9</td>
<td>13</td>
<td>12</td>
<td>19</td>
<td>1.31 [0.29, 5.89]</td>
</tr>
<tr>
<td>Bellomo 1995</td>
<td>12</td>
<td>16</td>
<td>139</td>
<td>218</td>
<td>1.71 [0.53, 5.47]</td>
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<tr>
<td>Mahajan 2006</td>
<td>46</td>
<td>95</td>
<td>25</td>
<td>37</td>
<td>0.45 [0.20, 1.00]</td>
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<tr>
<td>Watcharotone 2011</td>
<td>47</td>
<td>62</td>
<td>52</td>
<td>83</td>
<td>1.87 [0.90, 3.88]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>270</td>
<td>444</td>
<td></td>
<td></td>
<td>0.96 [0.53, 1.71]</td>
</tr>
<tr>
<td>Total events</td>
<td>159</td>
<td>260</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Heterogeneity: Tau² = 0.18; Chi² = 9.65, df = 7 (P = 0.21); I² = 27%
Test for overall effect: Z = 0.15 (P = 0.88)

B. Randomized Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>PD Events</th>
<th>PD Total</th>
<th>EBP Events</th>
<th>EBP Total</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arogundade 2005</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>Not estimable</td>
</tr>
<tr>
<td>George 2011</td>
<td>18</td>
<td>25</td>
<td>21</td>
<td>25</td>
<td>0.49 [0.12, 1.95]</td>
</tr>
<tr>
<td>Phu 2002</td>
<td>17</td>
<td>36</td>
<td>5</td>
<td>34</td>
<td>5.19 [1.64, 16.44]</td>
</tr>
<tr>
<td>Gabriel 2008</td>
<td>35</td>
<td>60</td>
<td>32</td>
<td>60</td>
<td>1.23 [0.60, 2.52]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>125</td>
<td>123</td>
<td></td>
<td></td>
<td>1.50 [0.46, 4.86]</td>
</tr>
<tr>
<td>Total events</td>
<td>70</td>
<td>58</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.77; Chi² = 7.29, df = 2 (P = 0.03); I² = 73%
Test for overall effect: Z = 0.68 (P = 0.50)
ISPD Guidelines/Recommendations
Peritoneal Dialysis for AKI

Cullis B. et al, Perit Dial Int. 2014; 34:494-517
Modality of ARRT

• Use continuous and intermittent RRT as complementary therapies in AKI patients. (Not Graded) (1A)
  
  *We suggest to use the RRT modality which is most advantageous for each individual patient in each specific clinical situation.* (ungraded)

• We suggest using CRRT, *or extended low-efficient dialysis* rather than standard intermittent RRT, for hemodynamically unstable patients. (2B)

• *In this patient group, we recommend to pay special attention to the connection procedure, to start with low blood and dialysate flows, and to consider using cooler dialysate temperatures.* (ungraded)

• We suggest using CRRT, *extended low-efficient dialysis or peritoneal dialysis* rather than intermittent RRT, for AKI patients with acute brain injury or other causes of increased intracranial pressure or generalized brain edema. (2B)


(CVV)HF, (CVV)HD, or (CVV)HDF?
# Hemofiltration compared to hemodialysis for acute kidney injury: systematic review and meta-analysis

*Critical Care* 2012, *16*:R146  
doi:10.1186/cc11458  
Jan O Friedrich (j.friedrich@utoronto.ca)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hemofiltration</th>
<th>Hemodialysis</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>1.1.1 Similar Dose Filtration vs Dialysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daud 2008 [25]</td>
<td>7</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Morgera 2004 [24]</td>
<td>6</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>OMAK 2012 [30]</td>
<td>22</td>
<td>39</td>
<td>20</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>60</td>
<td>61</td>
<td>35.1%</td>
</tr>
<tr>
<td>Total events</td>
<td>36</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00, Chi² = 6.11, df = 2 (P = 0.04); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.30 (P = 0.77)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.1.2 Similar Dose Filtration vs Dialysis-Filtration |
Chang 2009 [27]   |
Subtotal (95% CI) | 47    | 49   | 15.7% | 1.04 [0.72, 1.51] |
| Total events      | 26    | 26   | | | |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 0.22 (P = 0.82) |

1.1.3 Similar Dose (Intermittent) Dialysis-Filtration vs Dialysis |
Pettia 2001 [23]  |
Ratanarat 2012 [29] |
Subtotal (95% CI) | 48    | 50   | 14.4% | 1.22 [0.35, 4.22] |
| Total events      | 22    | 22   | | | |
| Heterogeneity: Tau² = 0.05, Chi² = 5.15, df = 1 (P = 0.02); I² = 0% |
| Test for overall effect: Z = 0.31 (P = 0.75) |

1.1.4 Filtration vs Higher-Dose Dialysis-Filtration |
Davenport 1983 [21] |
Saadat 2006 [26]   |
Subtotal (95% CI) | 110   | 115  | 34.0% | 1.34 [0.91, 1.96] |
| Total events      | 74    | 52   | | | |
| Heterogeneity: Tau² = 0.05, Chi² = 2.76, df = 1 (P = 0.10); I² = 64% |
| Test for overall effect: Z = 1.47 (P = 0.14) |

Total (95% CI) | 265   | 275  | 100.0% | 1.10 [0.80, 1.50] |
| Total events   | 157   | 136  | | | |
| Heterogeneity: Tau² = 0.06, Chi² = 13.06, df = 7 (P = 0.00); I² = 58% |
| Test for overall effect: Z = 0.87 (P = 0.38) |
| Test for subgroup differences: Chi² = 1.97, df = 3 (P = 0.68), P = 0% |

---

**Favours Hemofiltration**  **Favours Hemodialysis**
CVVH

replacement fluid →

blood circuit

filtrate

Filtrate rate max. 20% of blood flow with post-dilution
CVVH

replacement fluid

blood circuit

filtrate
Substantial reduction of effective delivered CRRT dose with predilution

<table>
<thead>
<tr>
<th></th>
<th>CVVH postdilution</th>
<th>CVVH predilution</th>
<th>CVVHDF postdilution</th>
<th>CVVHDF predilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>average urea clearance [ml/min]</td>
<td>31,7</td>
<td>22,6</td>
<td>32,1</td>
<td>27,0</td>
</tr>
</tbody>
</table>

- HF: 2 l/h replacement fluid
- HDF: 1 l/h dialysis fluid, 1 l/h replacement fluid, $Q_B=100$ ml/min
- theoretical clearance limit: 2000 ml/h = 33.3 ml/min
- post-dilution is substantially more effective than pre-dilution

Which ARRT „Dose“ ?
Multicenter RCT

1,124 patients with AKI

27 ICUs in USA

Nov. 2003 - July 2007

Intensive therapy:
IHD or SLED 6×/week
CVVHDF (predilution)
35 ml/kg×h

Less intensive therapy:
IHD or SLED 3×/week
CVVHDF (predilution)
20 ml/kg×h

No difference in survival
Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients

The RENAL Replacement Therapy Study Investigators

- Multicenter RCT
- 1,508 patients with AKI
- 35 ICUs in AU/NZ

**Intensive therapy:**
CVVHDF (postdilution)
40 ml/kg\times h

**Less intensive therapy:**
CVVHDF (postdilution)
25 ml/kg\times h

*No difference in survival*

*NEJM 2009; 361: 1627-38*
Results of RENAL—what is the optimal CRRT target dose?

John A. Kellum and Claudio Ronco

![Graph showing the relationship between delivered RRT intensity and survival.](image)
Hypophosphataemia:

- 461 patients (65.1%) in the higher-intensity group
- 396 patients (54.0%) in the less-intensive therapy group (P = 0.0001)
Hypophosphataemia in critically ill patients on RRT

- Occurs frequently
- Often undetected
- May result in significant clinical problems
  - Respiratory
  - Cardiovascular
  - Neuro-muscular
  - Haematological
- Should be treated with phosphate supplementation (i.v. or oral)
- Can be prevented by use of RRT fluids containing phosphate
Delivered dose of renal replacement therapy and mortality in critically ill patients with acute kidney injury

DOse REspONSE Multicentre International collaborative Initiative (DO-RE-MI Study Group)

- Prospective multicentre observational study in 30 ICUs in 8 countries from June 2005 to December 2007
- 553 AKI patients with RRT, including 338 who received CRRT only and 87 who received IRRT only
- No beneficial effect of more-intensive RRT dose on ICU survival, but shorter ICU stay and duration of mechanical ventilation
- Median **prescribed** CRRT dose: 34.3 ml/kg/hour (IQR = 27.3 to 42.9)
- Median **delivered** CRRT dose: 27.1 ml/kg/hour (IQR = 22.1 to 33.9).
Dose of Acute Renal Replacement Therapy

- **We do not recommend using Kt/V** as a measure of dose of dialysis in AKI when using intermittent or extended RRT in AKI. (1A)

- The dose of CRRT to be delivered should be prescribed before starting each session of CRRT as mL/kg/h filtration rate, dialysis volume or a combination thereof (not graded). We suggest regular assessment of the actually delivered dose. (1B)

- **We recommend delivering an effluent volume of 20–25 mL/kg/h** for post-dilution CRRT in AKI. (1A) This dose should be increased when pre-dilution is applied.

- **We recommend to adapt the administration of medication** in terms of dosing and timing, to the intensity of dialysis, taking into account pharmacokinetics and dialytic clearance of the drug.

Decision Tree for ARRT

AKI

- K↑↑↑, H↑↑↑; H₂O ↑↑; Clin. uraemia

- MOF; Oliguria; (Urea, crea ↑↑)

Start ARRT

- Volume = or ↓ MAP stable Pat. mobile

- Overhydrated MAP unstable Pat. immobile

Options:

- IHD daily
- PIRRT daily
- CRRT 25ml/kg×h⁻¹