CRRT: we should NOT start early

Miet Schetz, MD, PhD
Department of Intensive Care Medicine
Leuven - Belgium
**Evidence for early start?**

* = RCT

No control group without RRT

Unnecessary treatment?

More negative trials over past 5 years!

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**Study name** | **Subgroup within study** | **Statistics for each study** | **Odds ratio and 95% CI**
--- | --- | --- | ---
Bouman 2002* | Mixed | 1.375 | 0.487 | 3.884 | 0.601 | 0.548
Sugahara 2004* | Surgery | 0.028 | 0.003 | 0.231 | -3.318 | 0.001
Liu 2006 | Mixed | 0.773 | 0.460 | 1.298 | -0.974 | 0.330
Sabater 2008 | Mixed | 0.055 | 0.006 | 0.524 | -2.520 | 0.012
Bagshaw 2010* | Mixed | 1.563 | 0.933 | 2.619 | 1.897 | 0.060
Gettings 1999 | Surgery | 0.399 | 0.164 | 0.973 | -2.019 | 0.043
Elahi 2004 | Surgery | 0.800 | 0.273 | 2.341 | -0.407 | 0.684
Demirkilic 2004 | Surgery | 0.533 | 0.183 | 1.552 | -1.154 | 0.249
Andrade 2007 | Mixed | 0.100 | 0.019 | 0.515 | -2.752 | 0.006
Manche 2008 | Surgery | 0.051 | 0.010 | 0.256 | -3.623 | 0.000
Iyem 2009 | Surgery | 0.778 | 0.229 | 2.644 | -0.403 | 0.687
Shiao 2009 | Surgery | 0.260 | 0.110 | 0.614 | -3.075 | 0.002
Bagshaw 2009 adj | Mixed | 1.250 | 0.915 | 1.708 | 1.401 | 0.161
Wu 2007 adj | Surgical | 0.259 | 0.068 | 0.988 | -1.977 | 0.048
Carl 2010 adj | Mixed | 0.380 | 0.177 | 0.816 | -2.482 | 0.013

<table>
<thead>
<tr>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.446</td>
<td>0.276</td>
<td>0.723</td>
<td>-3.279</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Early RRT may be unnecessary RRT

RRT is not harmless

- RRT-induced hypotension → additional renal injury
- ….

Unnecessary Renal Replacement Therapy for Acute Kidney Injury is Harmful for Renal Recovery

Edward G. Clark* and Sean M. Bagshaw†
*Kidney Research Centre, Ottawa Hospital Research Institute, University of Ottawa and Division of Nephrology, The Ottawa Hospital, Ottawa, Ontario, Canada, and †Division of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada
RRT is not harmless

- RRT-induced hypotension -> renal injury
- Unselective nature of solute removal -> potential loss of essential substances (micro- and macronutrients, drugs, ...)
- Electrolyte disturbances (hypoK, hypoPh)
- Anticoagulation-related bleeding
- Infectious/mechanical complications of catheter
- Bioincompatibility (membrane exposure)
- Hypothermia (masking fever)
- Dysequilibrium syndrom
- Errors in fluid balance
- Costs
# Economic impact of early RRT?

<table>
<thead>
<tr>
<th></th>
<th>Stage 3 AKI</th>
<th>RRT</th>
<th>“unnecessary treatments”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoste 2006</td>
<td>1511</td>
<td>214 (14.2%)</td>
<td>1291</td>
</tr>
<tr>
<td>Kellum 2015</td>
<td>6024</td>
<td>1707 (28%)</td>
<td>4317</td>
</tr>
</tbody>
</table>

Hoste et al. Crit Care 2006; 10: R73  
Kellum et al. JASN 2015; 26: 2231-8
My arguments

1. Early RRT may be unnecessary 
   
   \[ \text{RRT} = \text{harm} \]
   
   \[ \rightarrow \text{harm of unnecessary RRT} \gg \text{the harm of late RRT} \]

2. ....
RRT for fluid overload

Observational trials show association between fluid overload at RRT initiation and mortality.

Bouchard et al. Kidney Intern 2009; 76: 422-7
Heung et al. Nephrol Dial Transplant 2012; 27: 956-61

However no trial has shown that prevention or reversal of this fluid overload with early RRT improves outcome
My arguments

1. Early RRT may be unnecessary RRT = harm
2. No evidence that early EC fluid removal improves outcome
We can wait for classical indications

We can wait for classical indications

RRT in 530 patients
RRT did not reduce mortality  OR 1.18 (0.94-1.50) (adjusted for risk factors)
RRT reduced mortality if complications  OR 0.75 (0.58-0.96)
My arguments

1. Early RRT may be unnecessary RRT = harm
2. No evidence that early EC fluid removal improves outcome
3. RRT may only improve outcome when complications are present (observational evidence)
We expect too much of our RRT's

Consequences of AKI?
- *measurable*: hyperkalemia, acidosis, fluid overload, azotemia
- *difficult to assess*: immune-mediated inflammatory consequences of tissue injury resulting in remote organ dysfunction (organ cross-talk)

Can these “unmeasurable effects” be corrected with RRT?

Lane et al. Nephrol Dial Transplant 2013; 28: 1634-47
Can RRT correct these effects?

In general we tend to expect too much of our RRT that only provides very rudimentary homeostasis without replacing the fine-tuning that is provided by the tubules nor the endocrine, metabolic and immune function of the natural kidney.
If our RRT’s were fantastic ...

How to explain that ...

1. Increasing the dose of RRT above current consensus level does not improve outcome neither in AKI nor in CKD
2. Mortality of AKI has not decreased despite improvement of RRT
3. ESRD patients are not all “fit and lively”
My arguments

1. Early RRT may be unnecessary RRT = harm
2. No proof that early EC fluid removal improves outcome
3. RRT may only improve outcome when complications are present (observational evidence)
4. Our current RRT’s are disappointing
We are not good at predicting RRT

Accuracy of NGAL for prediction of RRT

Meta-analysis of 10 studies in 1948 patients

AUROC of NGAL for prediction of RRT: 0.78

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>NGAL Cutoff (ng/mL)</th>
<th>Sensitivity (%, 95% confidence interval)</th>
<th>Specificity (%, 95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGAL to predict RRT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wagener et al, 2006</td>
<td>4 451 1 31 &gt;470</td>
<td>80.0 (29.9-99.0)</td>
<td>40.8 (29.8-52.7)</td>
</tr>
<tr>
<td>Wagener et al, 2008</td>
<td>5 150 3 268 &gt;680</td>
<td>62.5 (25.9-89.8)</td>
<td>64.1 (59.3-68.7)</td>
</tr>
<tr>
<td>Bennett et al, 2008</td>
<td>3 15 1 177 &gt;150</td>
<td>75.0 (21.9-98.7)</td>
<td>92.2 (87.2-95.4)</td>
</tr>
<tr>
<td>Koyner et al, 2008</td>
<td>5 28 2 37 &gt;480</td>
<td>71.4 (30.3-94.9)</td>
<td>56.9 (44.1-68.9)</td>
</tr>
<tr>
<td>Koyner et al, 2008 (u)</td>
<td>4 9 3 56 &gt;570</td>
<td>57.1 (20.3-88.2)</td>
<td>86.2 (74.8-93.1)</td>
</tr>
<tr>
<td>Nickolas et al, 2008</td>
<td>8 16 4 513 &gt;80</td>
<td>66.7 (35.4-88.7)</td>
<td>97.0 (95.0-98.2)</td>
</tr>
<tr>
<td>Wheeler et al, 2008</td>
<td>19 74 3 47 &gt;140</td>
<td>86.4 (64.0-96.4)</td>
<td>38.8 (30.2-48.2)</td>
</tr>
<tr>
<td>Cruz et al, 2009</td>
<td>13 99 2 187 &gt;150</td>
<td>86.7 (58.4-97.7)</td>
<td>65.4 (59.5-70.8)</td>
</tr>
<tr>
<td>Constantin et al, 2009</td>
<td>6 23 1 58 &gt;300</td>
<td>85.7 (42.0-99.3)</td>
<td>71.6 (60.3-80.8)</td>
</tr>
<tr>
<td>Haase-Fiellitz et al, 2009</td>
<td>3 0 1 96 &gt;340</td>
<td>75.0 (21.9-98.7)</td>
<td>100.0 (95.2-100.0)</td>
</tr>
</tbody>
</table>

- 70 true positive - 459 false positives
- PPV 13% - NPV 76%

My arguments against early start

1. Early RRT may be unnecessary RRT = harm
2. No evidence that early EC fluid removal improves outcome
3. RRT only improves outcome when complications are present (observational evidence)
4. Our current RRT’s are disappointing
5. We are bad in predicting need for RRT

“Less Is More”: The New Paradigm in Critical Care
My suggestions for clinical practice

Table 1 Absolute and relative indications for commencing or not commencing RRT

<table>
<thead>
<tr>
<th>Reasons to start</th>
<th>Reasons not to start</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute</td>
<td></td>
</tr>
<tr>
<td>Severe hyperkalemia</td>
<td>Futile therapy</td>
</tr>
<tr>
<td>Severe acidosis</td>
<td></td>
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<tr>
<td>Organ dysfunction due to diuretic-resistant fluid overload</td>
<td></td>
</tr>
<tr>
<td>Uraemic complications (pericarditis, encephalopathy etc.)</td>
<td></td>
</tr>
<tr>
<td>Life-threatening intoxications with substances which</td>
<td></td>
</tr>
<tr>
<td>can be dialysed (low protein binding (&lt;50 %), low volume</td>
<td></td>
</tr>
<tr>
<td>of distribution and low molecular weight)</td>
<td></td>
</tr>
<tr>
<td>Relative</td>
<td></td>
</tr>
<tr>
<td>Diuretic-resistant fluid overload</td>
<td>Oliguria without clinically important fluid overload</td>
</tr>
<tr>
<td>Limited tolerance to fluid overload</td>
<td>Sufficient cardiocirculatory and respiratory reserve</td>
</tr>
<tr>
<td></td>
<td>to tolerate fluid overload</td>
</tr>
<tr>
<td>Rapidly worsening kidney function</td>
<td>Slow deterioration in kidney function</td>
</tr>
<tr>
<td>Underlying disease not rapidly reversible</td>
<td>Potential for short-term reversibility of the underlying disease</td>
</tr>
<tr>
<td>Reduced risk of harm from RRT</td>
<td>Potential harm of RRT (may include unavailability of CRRT)</td>
</tr>
<tr>
<td>Furosemide stress test with UO 2 h &lt; 200 mL</td>
<td>Furosemide stress test with UO 2 h &gt; 200 mL</td>
</tr>
</tbody>
</table>