Renal Replacement Therapy
When and how much...

M. Joannidis
Medizinische Intensivstation
Universitätsklinik für Innere Medizin I
Medizin Universität Innsbruck
Research

Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury

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Received: 8 Dec 2006 Revised: 28 Dec 2006 Received: 9 Feb 2007 Accepted: 1 Mar 2007 Published: 1 Mar 2007

This article is online at: http://ccforum.com/content/11/2/R31
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Early vs late start of RRT

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Study Design</th>
<th>Predialysis BUN (mg/dl)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Early</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Late</td>
<td></td>
</tr>
<tr>
<td>Parsons et al.</td>
<td>(6)</td>
<td>1961</td>
<td>33</td>
<td>Cohort with historical control</td>
<td>120 to 150</td>
<td>25</td>
</tr>
<tr>
<td>Fischer et al.</td>
<td>(7)</td>
<td>1966</td>
<td>162</td>
<td>Cohort with historical control</td>
<td>152</td>
<td>51</td>
</tr>
<tr>
<td>Kleinknecht et al.</td>
<td>(8)</td>
<td>1972</td>
<td>320</td>
<td>Cohort with historical control</td>
<td>93</td>
<td>29</td>
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<tr>
<td>Conger et al.</td>
<td>(9)</td>
<td>1975</td>
<td>18</td>
<td>Case-control</td>
<td>50</td>
<td>20</td>
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<tr>
<td>Getting et al.</td>
<td>(10)</td>
<td>1999</td>
<td>100</td>
<td>Retrospective cohort</td>
<td>42.6</td>
<td>61</td>
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<tr>
<td>Bouman et al.</td>
<td>(16)</td>
<td>2002</td>
<td>65</td>
<td>Randomized trial</td>
<td>48</td>
<td>31</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>105</td>
<td>25</td>
</tr>
</tbody>
</table>

*Case patients and control subjects differed with respect to both the timing of initiation of dialysis and the dose of dialysis delivered.

Liu et al, CJASN 2006
Initiation of CRRT after the “millennium party”

Large (n\(>\)100), randomized trials renal replacement therapy in ICU patients with AKI endpoint - mortality

- BUN 50 mg/dl, Crea 3.5 mg/dl (Ronco C, Lancet 2000)
- BUN 85 mg/dl, Crea 4.5 mg/dl (Mehta R, Kidney Int 2001)
- BUN 90 mg/dl, Crea 5.0 mg/dl (Schiffl H, NEJM 2002)
- BUN 83 mg/dl, Crea 4.3 mg/dl (Saudan P, Kidney Int 2006)
- BUN 76 mg/dl, Crea 4.3 mg/dl (Tolwani A, JASN 2008)
- BUN 66 mg/dl (ATN-VA, NEJM 2008)
- BUN 63 mg/dl, Crea 3.4 mg/dl (Faulhaber-;NDT 2009)
- BUN 64 mg/dl, Crea 3.4 mg/dl (RENAL, NEJM 2009)
Timing of Replacement Therapy for Acute Renal Failure After Cardiac Surgery

Ufuk Demirkılıç, M.D.,* Erkan Kuralay, M.D.,* Müjdat Yenicesu, M.D.,† Kayser Çağlar, M.D.,† Bilgehan Savaş Öz, M.D.,* Faruk Cingöz, M.D.,* Celalettin Günay, M.D.,* Vedat Yıldırım, M.D.,# Süleyman Ceylan, M.D.,‡ Mehmet Arslan, M.D.,* Abdulgaffar Vural, M.D.,† Harun Tatar, M.D.*

*Cardiovascular Surgery Department; †Nephrology Department; ‡Public Health Department; #Anesthesiology Department, Etkik, Ankara, Turkey

J Card Surgery 2004; 19:17-20

Group 1 (late):
- crea > 5mg/dl or K > 5.5 mmol/l

Group 2 (early):
- Uo < 100ml for 8h despite furosemide 50mg

CVVHDF dose?
# Timing of Replacement Therapy for Acute Renal Failure After Cardiac Surgery

## TABLE 2
### Intraoperative and Postoperative Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n = 27)</th>
<th>Group 2 (n = 34)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean CPB time (min)</td>
<td>72.1 ± 16.6</td>
<td>79.8 ± 9.1</td>
<td>0.055*</td>
</tr>
<tr>
<td>Mean cross-clamp time (min)</td>
<td>44.7 ± 11</td>
<td>51 ± 7.9</td>
<td>0.010*</td>
</tr>
<tr>
<td>Inotropy requirement</td>
<td>18</td>
<td>22</td>
<td>0.873*</td>
</tr>
<tr>
<td>IAB</td>
<td>8</td>
<td>13</td>
<td>0.482*</td>
</tr>
<tr>
<td>Mechanical ventilation time (day)</td>
<td>3 ± 2.1</td>
<td>1 ± 0.6</td>
<td>0.014*</td>
</tr>
<tr>
<td>CVVHDF initiation after surgery (day)</td>
<td>2.56 ± 1.67</td>
<td>0.88 ± 0.33</td>
<td>0.0001*</td>
</tr>
<tr>
<td>CVVHDF time (day)</td>
<td>4.56 ± 1.31</td>
<td>4.32 ± 1.45</td>
<td>0.512*</td>
</tr>
<tr>
<td>ICU stay (day)</td>
<td>12.41 ± 3.44</td>
<td>7.85 ± 1.26</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Hospital stay (day)</td>
<td>20.9 ± 7.0</td>
<td>15.4 ± 4.0</td>
<td>0.016*</td>
</tr>
<tr>
<td>ICU mortality (%)</td>
<td>48.1 (13/27)</td>
<td>17.6 (6/34)</td>
<td>0.014*</td>
</tr>
<tr>
<td>Hospital mortality (%)</td>
<td>55.5 (15/27)</td>
<td>23.5 (8/34)</td>
<td>0.016*</td>
</tr>
</tbody>
</table>

\* = Mann-Whitney U test; \* = chi-squared test; CPB = cardiopulmonary bypass; IAB = intra-aortic balloon; ICU = intensive care unit; CVVHDF = continuous veno-venous hemodiafiltration.
Timing of RRT in Acute Renal Failure -
Meta Analysis

Seabra VF. AJKD 2008

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Risk ratio (95% CI)</th>
<th>No. of events</th>
<th>Early RRT</th>
<th>Late RRT</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conque (1979)</td>
<td>0.47 (0.18, 1.19)</td>
<td>1.16</td>
<td>5/17</td>
<td>7/15</td>
<td>3.2</td>
</tr>
<tr>
<td>Pursani (1997)</td>
<td>0.76 (0.34, 3.35)</td>
<td>11/56</td>
<td>11/36</td>
<td>5/17</td>
<td>4.4</td>
</tr>
<tr>
<td>Bournaz (2002)</td>
<td>1.26 (0.69, 2.36)</td>
<td>0.10</td>
<td>1/21</td>
<td>7/23</td>
<td>4.0</td>
</tr>
<tr>
<td>Koo (2006)</td>
<td>0.55 (0.32, 0.94)</td>
<td>0.64</td>
<td>12/43</td>
<td>30/159</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>0.64 (0.39, 1.05)</td>
<td>31/125</td>
<td>59/145</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Each study has another definition of EARLY!!!
Should we use RIFLE Criteria for initiation?

GFR Criteria*  Urine Output Criteria

Risk
- Increased SCreat x1.5 or GFR decrease > 25%
- Increased SCreat x2 or GFR decrease > 50%

Injury
- Increase SCreat x3 or GFR decrease 75% OR SCreat ≥4mg/dl

Failure
- Persistent ARF** = complete loss of kidney function > 4 weeks
- End Stage Kidney Disease (> 3 months)

Loss

ESKD

Urine Output Criteria
- UO < .5ml/kg/h x 6 hr
- UO < .5ml/kg/h x 12 hr
- UO < .3ml/kg/h x 24 hr or Anuria x 12 hrs

Critical Care

Bellomo R, Crit Care 2004
Late initiation of renal replacement therapy is associated with worse outcomes in acute kidney injury after major abdominal surgery.

**Further problems:**
- CKD 55% vs 28% p<0.008
- Baseline Crea 2.1 vs 1.3 mg/dl

Shiao C-C, Crit Care 2009
Should we use RIFLE Criteria for initiation?

No association between RIFLE stage at start of CRRT and survival!

Maccariello et al, Intensive Care Med 2007
**RIFLE classification in patients with acute kidney injury in need of renal replacement therapy**

<table>
<thead>
<tr>
<th>Indications for RRT$^a$</th>
<th>All patients (n = 214)</th>
<th>Risk (n = 54, 25%)</th>
<th>Injury (n = 58, 27%)</th>
<th>Failure (n = 102, 48%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azotemia</td>
<td>114 (53%)</td>
<td>19 (35%)</td>
<td>34 (59%)</td>
<td>61 (60%)</td>
</tr>
<tr>
<td>Hypervolemia</td>
<td>77 (50%)</td>
<td>22 (41%)</td>
<td>32 (55%)</td>
<td>53 (52%)</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>90 (42%)</td>
<td>33 (61%)</td>
<td>17 (29%)</td>
<td>40 (39%)</td>
</tr>
<tr>
<td>Oliguria</td>
<td>45 (21%)</td>
<td>0</td>
<td>6 (10%)</td>
<td>39 (38%)</td>
</tr>
<tr>
<td>Hyperkalemia$^b$</td>
<td>18 (8%)</td>
<td>1 (2%)</td>
<td>54 (7%)</td>
<td>13 (13%)</td>
</tr>
<tr>
<td>Dysnatremia</td>
<td>11 (5%)</td>
<td>3 (6%)</td>
<td>5 (9%)</td>
<td>3 (3%)</td>
</tr>
</tbody>
</table>

Maccariello et al, Intensive Care Med 2007
What are relevant parameters for initiation?

- Urea?
- Creatinine?
- Urinary Output?
- Volume overload?
„Unguided fluid administration may be hazardous…“
Fluid Management in ALI

<table>
<thead>
<tr>
<th>Fluid balance / week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conserv. Strategy (n=503):</td>
</tr>
<tr>
<td>-136 (+ 491) ml</td>
</tr>
<tr>
<td>Liberal Strategy (n=498):</td>
</tr>
<tr>
<td>+ 6992 (+502) ml</td>
</tr>
</tbody>
</table>

ARDS Clinical Network Trial, NEJM 2006
Effect on fluid overload on survival (PICARD Study)

Mortality rate by final fluid accumulation relative to baseline weight and stratified by dialysis status

610 Pat. (65% RRT), 5 Academic Centres

Bouchard J et al, Kidney Int 2009
Start of CRRT in SEPSIS

- AKI
- Vasopressors
- Intubation
- IRV

Death
Clinical trials - CRRT in Sepsis

• randomized trial with 24 pt. in early septic shock
• 48 h isovolemic CVVH 2L/h vs. stand. med. treatment
• 72 h observation period
• primary parameters:
  – C3a + C5a, interleukins 6, 8 + 10, TNF
  – MODS

Cole L et al., Crit Care Med 2002
Clinical trials - CRRT in Sepsis

- randomized trial with 24 pt. in early septic shock
- 48 h isovolemic CVVH 2L/h vs. stand. med. treatment
- 72 h observation period
- primary parameters:
  - C3a + C5a, interleukins 6, 8 + 10, TNF
  - MODS
- No significant changes in cytokines or C3a + C5a by CVVH
- MODS – no difference between both groups.
- CVVH does not result in improvement of oxygenation or hemodynamics

Cole L et al., Crit Care Med 2002
Clinical trials - CRRT in Sepsis

- randomized trial with 24 pt. in early septic shock
- 48 h isovolemic CVVH 2L/h vs. stand. med. treatment
- 72 h observation period
- primary parameters:
  - C3a + C5a, interleukins 6, 8 + 10, TNF
  - MODS
- No significant changes in cytokines or C3a + C5a by CVVH
- CVVH does not result in improvement of oxygenation or hemodynamics

“CVVH cannot be recommended as an adjunct to the treatment of septic shock unless severe acute renal failure is present”

Cole L et al., Crit Care Med 2002
Impact of continuous venovenous hemofiltration on organ failure during the early phase of severe sepsis. A randomized controlled trial.

Parameters at time of Randomisation:

Crea = 2.1 mg/dl
BUN= 42 mg/dl
pH= 7.33
UO= 1.5 l/d (~0.8 ml/kg/h)

Payen D, Crit Care Med 2009
Impact of continuous venovenous hemofiltration on organ failure during the early phase of severe sepsis. A randomized controlled trial

Payen D, Crit Care Med 2009
Impact of continuous venovenous hemofiltration on organ failure during the early phase of severe sepsis. A randomized controlled trial

These data suggest that early application of standard continuous venovenous hemofiltration is deleterious in severe sepsis and septic shock. This study does not rule out an effect of high-volume hemofiltration (>35 mL/kg/hr) on the course of sepsis.

Payen D, Crit Care Med 2009
Early RRT ...?
Consider Adverse Effects of RRT

- Loss of trace elements (e.g. selenium)
- Loss of vitamins (e.g. thiamine, vit C)
- Loss of nutrients (AA)
- Loss of heat (is cooling good for sepsis?)
- Complications with catheter
- Anticoagulation (e.g. heparin)
Murphy’s law

Never try to repair something that is not broken....
Initiation of CRRT
A worldwide practice survey (B.E.S.T kidney)

- Oliguria/anuria 70.2%
- High urea/creatinine 53.0%
- Metabolic acidosis 43.6%
- Fluid overload 36.7%

Uchino et al, Intensive Care Med 2007
Dose of RRT?
2007

The world of RRT
Dose of RRT 2007

**CVVH**
35 ml/kg/h (80%)
(Ronco C, Lancet 2000)

**Daily IHD**
weekly KT/V 5.8
(Schiffl H, NEJM 2002)

**CVVHDF**
42 ml/kg/h
(Saudan P, Kidney Int 2006)
Dose in RRT
(Questionaire in Vlcezza course of Critical Care Nephrology)

![Pie charts showing urea and sepsis K target doses](image)

n=1124

IHD daily or SLED or CVVHDF 35 ml/kg/h

IHD every other day or SLED or CVVHDF 20 ml/kg/h (~22 ml/kg/h delivered)
Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients

The RENAL Replacement Therapy Study Investigators*
Numbers of Patients Enrolled in the Study, Randomly Assigned to a Treatment Group, and Included in the Analysis

Kaplan-Meier Estimates of the Probability of Death


**Indications:**

- 60% oliguria (<400ml/d)
- 40-50% crea>3.4 mg/dl, BUN>70mg/dl
- 44% severe organ edema
- 35% acidemia
### RENAL-specific aspects

<table>
<thead>
<tr>
<th></th>
<th>Higher Intensity</th>
<th>Lower Intensity</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>66%</td>
<td>64%</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>64.7</td>
<td>64.4</td>
<td></td>
</tr>
<tr>
<td>Time in ICU before</td>
<td>48.4 h</td>
<td>54.5 h</td>
<td></td>
</tr>
<tr>
<td>randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>80.8 kg</td>
<td>80.5 kg</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>49.9%</td>
<td>48.9%</td>
<td></td>
</tr>
<tr>
<td>Dose delivered</td>
<td>84%</td>
<td>88%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>~34 ml/kg/h</td>
<td>~22 ml/kg/h</td>
<td></td>
</tr>
<tr>
<td>Filters uses daily</td>
<td>0.93</td>
<td>0.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>65%</td>
<td>54%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
CRRT Dose: how much is enough?

Dose ml/kg/h

- CVVHDF
- CVVH

< 1999 2000 2006 2008 2009

Ronco (300) Saudan (200) ATN (1100) RENAL (1500)
DIALYSISSDOSE AND SEVERITY OF DISEASE

Paganini, Am J Kidney Dis 1996
Should we apply a different dose in severe sepsis/septic shock?
Sepsis

Modulation of sepsis by removal of mediators??

SIRS

CARS

IL-1
IL-6
TNF
PAF
endothelin
C3a/C5

IL-10
sTNFR
IL-2 ra
Elimination (%) in Correlation to Half-life und Elimination-coefficient

<table>
<thead>
<tr>
<th>Filtrate</th>
<th>S.C.</th>
<th>15 min</th>
<th>30 min</th>
<th>60 min</th>
<th>120 min</th>
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<tbody>
<tr>
<td>1 l/h</td>
<td>0,1</td>
<td>0,3</td>
<td>0,6</td>
<td>1,2</td>
<td>2,4</td>
</tr>
<tr>
<td>1 l/h</td>
<td>0,25</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>2 l/h</td>
<td>0,1</td>
<td>0,6</td>
<td>1,2</td>
<td>2,4</td>
<td>4,8</td>
</tr>
<tr>
<td>2 l/h</td>
<td>0,25</td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>3 l/h</td>
<td>0,1</td>
<td>0,9</td>
<td>1,8</td>
<td>3,6</td>
<td>7,2</td>
</tr>
<tr>
<td>3 l/h</td>
<td>0,25</td>
<td>3</td>
<td>6</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>8 l/h</td>
<td>0,25</td>
<td>8</td>
<td>16</td>
<td>32</td>
<td>68</td>
</tr>
</tbody>
</table>

Kierdorf H, Kidney Int 1999
## Size, Kinetics und Elimination of Cytokines

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Molecular-weight (kD)</th>
<th>Half-life (min)</th>
<th>Sieving-coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF</td>
<td>Monomer 17</td>
<td>6-7</td>
<td>0-1,0</td>
</tr>
<tr>
<td></td>
<td>Trimer 52</td>
<td>10-17, ~15</td>
<td>0-0,2</td>
</tr>
<tr>
<td>IL-1</td>
<td>18</td>
<td>6-10</td>
<td>0,07 - 0,42</td>
</tr>
<tr>
<td>IL-2</td>
<td>~ 10</td>
<td>?</td>
<td>0,1 - 0,25</td>
</tr>
<tr>
<td>IL-6</td>
<td>26</td>
<td>6-10</td>
<td>0,01 – 0,32</td>
</tr>
<tr>
<td>IL-8</td>
<td>6-8</td>
<td>~ 6</td>
<td>0,0 – 0,48</td>
</tr>
</tbody>
</table>

Kierdorf H, Kidney Int 1999
### Elimination (%) in Correlation to Half-life und Elimination-coefficient

<table>
<thead>
<tr>
<th>Filtrate</th>
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<tr>
<td>1 l/h</td>
<td>0,25</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>2 l/h</td>
<td>0,1</td>
<td>0,6</td>
<td>1,2</td>
<td>2,4</td>
<td>4,8</td>
</tr>
<tr>
<td>2 l/h</td>
<td>0,25</td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>3 l/h</td>
<td>0,1</td>
<td>0,9</td>
<td>1,8</td>
<td>3,6</td>
<td>7,2</td>
</tr>
<tr>
<td>3 l/h</td>
<td>0,25</td>
<td>3</td>
<td>6</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>8 l/h</td>
<td>0,25</td>
<td>8</td>
<td>16</td>
<td>32</td>
<td>68</td>
</tr>
</tbody>
</table>

Kierdorf H, Kidney Int 1999
Cytokine plasma-concentrations during CVVHF

Filter exchanged

CVVH UF=2L/h

De Vriese AN, JASN 1999
Clinical trials -
CRRT in Sepsis

Table 2. Median concentrations of mediators at baseline and 72 hrs (interquartile range)

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Hemofiltration</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>72 Hrs</td>
</tr>
<tr>
<td>C3a</td>
<td>410 (325)</td>
<td>200 (260)</td>
</tr>
<tr>
<td>C5a</td>
<td>31 (25)</td>
<td>19 (16)</td>
</tr>
<tr>
<td>IL-6</td>
<td>1296 (217)</td>
<td>370 (543)</td>
</tr>
<tr>
<td>IL-8</td>
<td>97 (378)</td>
<td>49 (43)</td>
</tr>
<tr>
<td>IL-10</td>
<td>21 (357)</td>
<td>47 (383)</td>
</tr>
<tr>
<td>TNF-α</td>
<td>337 (156)</td>
<td>345 (91)</td>
</tr>
</tbody>
</table>

Cole L et al., Crit Care Med 2002
The impact of long-term haemofiltration (continuous veno-venous haemofiltration) on cell-mediated immunity during endotoxaemia

CVVH 35 ml/kg/h, porcine ETx model

Mortality in the Prespecified Subgroups and among All Patients

<table>
<thead>
<tr>
<th>Prespecified Subgroup</th>
<th>Higher Intensity (N=721)</th>
<th>Lower Intensity (N=743)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with criteria for sepsis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>168/359 (46.8)</td>
<td>186/363 (51.2)</td>
<td>0.84 (0.62–1.12)</td>
</tr>
<tr>
<td>No</td>
<td>154/362 (42.5)</td>
<td>145/379 (38.3)</td>
<td>1.19 (0.89–1.60)</td>
</tr>
<tr>
<td>Patients with at least one nonrenal organ failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>799/628 (47.6)</td>
<td>1066/649 (47.7)</td>
<td>1.02 (0.82–1.37)</td>
</tr>
<tr>
<td>No</td>
<td>23/93 (24.7)</td>
<td>25/93 (26.9)</td>
<td>0.89 (0.46–1.72)</td>
</tr>
<tr>
<td>Patients with SOFA cardiovascular score of 3 or 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>247/510 (48.4)</td>
<td>254/546 (46.5)</td>
<td>1.08 (0.85–1.37)</td>
</tr>
<tr>
<td>No</td>
<td>74/210 (35.2)</td>
<td>75/194 (38.7)</td>
<td>0.86 (0.58–1.29)</td>
</tr>
<tr>
<td>Patients with eGFR &lt;60 ml/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>114/250 (45.6)</td>
<td>105/222 (47.3)</td>
<td>0.93 (0.65–1.34)</td>
</tr>
<tr>
<td>No</td>
<td>81/157 (51.6)</td>
<td>81/185 (43.8)</td>
<td>1.37 (0.89–2.10)</td>
</tr>
<tr>
<td>Missing</td>
<td>127/314 (40.5)</td>
<td>146/336 (43.5)</td>
<td>0.88 (0.65–1.21)</td>
</tr>
<tr>
<td>Death from any cause by day 90</td>
<td>322/721 (44.7)</td>
<td>332/743 (44.7)</td>
<td>1.00 (0.81–1.23)</td>
</tr>
</tbody>
</table>

Should we apply a different dose in severe sepsis/septic shock?

rather not...
Summary

• Dose:
  1) „individualised“ dose!
  2) minimal dose:
     ➔ >20-25ml/kg/h CRRT
     ➔ ≥1.3 Kt/V (4h) IHD

• Initiation:
  ➔ early:
     • oliguria (persistent!!)
     • severe organ edema
     • acidosis
     • BUN >50-80 mg% (?)

-> but not too early!
Thank you for your attention
The Hannover Dialysis Outcome study: comparison of standard versus intensified extended dialysis for treatment of patients with acute kidney injury in the intensive care unit

**SLED daily (SED)**
- BUN 60-75 mg/dl
- \( N = 76 \)

**SLED intensified (IED)**
- BUN < 45 mg/dl
- \( n = 81 \)

The VA/NIH Acute Renal Failure Trial Network

Delivered Dialysis Dose

Delivered CVVHDF Dose

Discontinuation of continuous renal replacement therapy (B.E.S.T kidney)

Figure 3. Impact of diuretics use on predictive ability of urine output. The area under the receiver operating characteristics curve of urine output for successful discontinuation of continuous renal replacement therapy was 0.671 (0.585–0.750) with diuretics and 0.845 (0.799–0.883) without diuretics. Urine output of 436 mL/day for patients without diuretics and of 2330 mL for those with diuretics had the highest accuracy.

Uchino et al, Crit Care Medicine 2009
The big bang of hemofiltration: The beginning of a new era in the third millennium for extra-corporeal blood purification!

P.M. HONORE¹, O. JOANNES-BOYAU², L. MERSON², W. BOER², V. PIETTE¹, A.-C. GALLOY¹, G. JANVIER²

¹ ICU Department of Acute Medicine, St-Pierre Para-Universitary Hospital, Ottignies Louvain-La-Neuve - Belgium
² Department of Anesthesiology and Reanimation II, University Hospital of Bordeaux, University
Haut Leveque, Pessac - France
³ ICU and Nephrology Departments, Atidum Hospital, Bordeaux - France

more filtration volume ...

bigger pores ....

better survival ...!??!
High-volume HF (HVH)

- 11 patients in septic shock
- Design: randomized, cross-over

HVHF (8h)
QB=300 ml/min, UF 6L/h
1,6 m² AN 69 (polyacrylonitril)

Standard HF (8h)
QB=200 ml/min, UF 1L/h
1,2 m² AN 69 (polyacrylonitril)

reductions in C3a, C5a, IL-10 (~ 80%)
reduced requirements of vasopressors

Cole L, Int. Care Med 2001
IL6 and Il1-ra in septic shock treated with HVH

- RCT: CVVH (2l/h, n=18) vs. (6l/h, n=15) over 6 h

Ghani et al, Nephrology 2006

<table>
<thead>
<tr>
<th></th>
<th>HVHF group (n = 15)</th>
<th>CVVH group (n = 18)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>IQR</td>
<td>Median</td>
</tr>
<tr>
<td>Se IL-1-ra levels at baseline (pg/mL)</td>
<td>6783.01</td>
<td>197.0</td>
<td>6783.01</td>
</tr>
<tr>
<td>Difference in serum IL-1-ra levels (pg/mL)</td>
<td>(− reduction, + increase)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 3 h</td>
<td>−4.9</td>
<td>104.39</td>
<td>+176.17</td>
</tr>
<tr>
<td>After 6 h</td>
<td>−41.35</td>
<td>232.80</td>
<td>+82.43</td>
</tr>
<tr>
<td>After 24 h</td>
<td>+24.75</td>
<td>348.0</td>
<td>+94.27</td>
</tr>
</tbody>
</table>

CVVH, continuous venovenous haemofiltration; HVHF, high-volume haemofiltration; IQR, interquartile range. Normal ranges: IL-1-ra 106–1552 pg/mL.

⇒ significant reduction of IL-6 after HVH

Ghani et al, Nephrology 2006
Ex vivo Sieving Coefficients of Cytokines

HF, UF=1L/h, t=2h

data from Uchino et al.
Pilot Study of CRRT with High Cut-off Membranes (~60kD) on the need for norepinephrine in septic Patients with acute renal failure

Morgera S et.al , Critical Care Medicine 2006
Pilot Study of CRRT with High Cut-off Membranes (~60kD) on the need for norepinephrine in septic Patients with acute renal failure

Morgera S et al., Critical Care Medicine 2006
Urea-distribution volume and total body water in critically ill patients

Ikizler F, Kidney Int 2004
Timing and Dosing

- ↑ Urea production rate
- ↑ Catabolic state
- ↓ Volume of distribution
Timing and Dosing

CRRT

higher volume of distribution

higher dose
Timing and Dosing

Timing and Dosing

BUN time

very early start

earlier start

CRRT

very early start

time

BUN
Timing and Dosing

Urea production rate
Catabolic state
volume of distribution (urea)

volume of distribution (urea)
higher dose
earlier start