Prevention and nondialytic treatment of ARF

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Renal Division
University Hospital
Ghent, Belgium
Acute renal failure (ARF) is a syndrome defined as a sudden decline in glomerular filtration rate, clinically characterised by an abrupt increase in blood urea and serum creatinine.
RIFLE Criteria

Figure 1

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

- **Injury**
  - Increased SCreat x2 or GFR decrease > 50%

- **Failure**
  - Increase SCreat x3 GFR decrease 75% OR SCreat ≥4mg/dl
    - Acute rise ≥0.5mg/dl
  - Persistent ARF** = complete loss of kidney function > 4 weeks

- **Loss**
  - End Stage Kidney Disease (>3 months)

- **ESKD**

**GFR Criteria**
- 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

**High Sensitivity**

**High Specificity**
Relation between RIFLE and outcome

Figure 1

Flow chart of the clinical course of patients until the maximum RIFLE class. Data expressed as patient numbers who were identified at each level, and the percentage of the total number of patients. Patients who appear to skip a grade (class risk or class injury) do so because they did not remain at a transition state for at least 24 hours. 'Ever Risk' and 'Ever Failure' refers to the number of patients who could be identified at this stage. AKI, acute kidney injury; ICU, intensive care unit; RIFLE, Risk, Injury, Failure, Loss, and End-stage Kidney Disease.

Hoste et al, Crit Care Med, 2006
Relation between RIFLE and outcome

Kaplan-Meier curves for survival (inhospital) by maximum RIFLE class. Patients discharged alive were censored. Log-rank statistic, \( P < 0.001 \).

AKI, acute kidney injury; RIFLE\(_{\text{max}}\), maximum Risk, Injury, Failure, Loss, and End-stage Kidney Disease (RIFLE) class during the intensive care unit stay (days).

Hoste et al, Crit Care Med, 2006
An assessment of the RIFLE criteria for acute renal failure in critically ill HIV-infected patients
José António Lopes¹, Joana Fernandes², Sofia Jorge¹, José Neves², Francisco Antunes² and Mateus Martins Prata¹

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Acute Renal Disease, as Defined by the RIFLE Criteria, Post-Liver Transplantation

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Corresponding author: Dr. Aisling O’Riordan, aisling32@ireland.com

An assessment of the rifle criteria for acute renal failure in severely burned patients

Sir
30-day Mortality and Change in SCr (ΔCrea) within 48 h after Cardiac Surgery

1. The rise/fall in serum creatinine always lags behind changes in GFR
2. Estimated GFR formulas do NOT work in ICU
Early detection of ARF by Cystatin C

Changes in cystatin C were able to detect the onset of ARF one to two days earlier than comparable changes in serum creatinine:

1. RIFLE- R (≥ 50 % increase): 1.5 ± 0.6 days earlier
2. RIFLE- I (≥ 100 % increase): 1.2 ± 0.9 days earlier
3. RIFLE- F (≥ 200 % increase): 1.0 ± 0.6 days earlier

<table>
<thead>
<tr>
<th>Definition of AF</th>
<th>Area under the ROC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day - 2</td>
</tr>
<tr>
<td>≥ 50 % increase</td>
<td>0.82</td>
</tr>
<tr>
<td>≥ 100 % increase</td>
<td>0.92</td>
</tr>
<tr>
<td>≥ 200 % increase</td>
<td>0.97</td>
</tr>
</tbody>
</table>

New urinary biomarkers for the early detection of acute kidney disease

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Assay</th>
<th>Associated injury</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIM-1</td>
<td>ELISA</td>
<td>Ischemic ATN and nephrotoxins</td>
<td>Han et al. [41], Ichimura et al. [42•]</td>
</tr>
<tr>
<td>NGAL</td>
<td>Western blot</td>
<td>Ischemic ATN and nephrotoxins</td>
<td>Mishra et al. [43•,44•]</td>
</tr>
<tr>
<td>NHE3</td>
<td>Immunoblot</td>
<td>Ischemic ATN, prerenal azotemia and postrenal AKI</td>
<td>du Cheyron et al. [45•]</td>
</tr>
<tr>
<td>Cytokines (IL-6, IL-8, IL-18)</td>
<td>ELISA</td>
<td>AKI and delayed graft function</td>
<td>Kwon et al. [46•], Panikh et al. [47•]</td>
</tr>
<tr>
<td>Cyr61</td>
<td>Western blot</td>
<td>Ischemic ATN</td>
<td>Muramatsu et al. [48]</td>
</tr>
<tr>
<td>Actin</td>
<td>Western blot</td>
<td>Ischemic ATN and delayed graft function</td>
<td>Kwon et al. [46•]</td>
</tr>
<tr>
<td>α-GST</td>
<td>ELISA</td>
<td>PT injury, cyclosporine A toxicity, early CRI</td>
<td>Usuda et al. [10], Branten et al. [49]</td>
</tr>
<tr>
<td>π-GST</td>
<td>ELISA</td>
<td>DT injury, acute rejection, later CRI</td>
<td>Usuda et al. [10], Branten et al. [49]</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>Immunonephelometric immunoassay</td>
<td></td>
<td>Herget-Rosenthal et al. [28], Randers et al. [80], Coll et al. [81], Dharnidharka et al. [82], Shimizu-Tokiwa et al. [83], Christensson et al. [84]</td>
</tr>
</tbody>
</table>

Neutrophil gelatinase associated lipocalin

Han, Bonventre, Current Opin Crit Care 2004, 10:476–482
Urinary NGAL (Neutrophil Gelatinase Associated Lipocalin) and ischemia/reperfusion injury in the mouse

Mishra et al, JASN, 2003
Urine NGAL excretion post cardiac surgery in children

Neutrophil gelatinase associated lipocalin

Biomarkers and ARF in ICU

Odd’s ratio for dialysis and/or death

Liangos et al. JASN, 2007
Biomarkers and ARF in ICU

Maximal effect

%  

0 10 20 30 40 50 60 70 80 90 100  

0.5 1 3 5 10 20 30  

Hours after insult  

σ  β  α
Urinary indices in differential diagnosis between acute prerenal failure and acute tubular necrosis

<table>
<thead>
<tr>
<th>Prerenal failure</th>
<th>ATN</th>
</tr>
</thead>
<tbody>
<tr>
<td>high Uosm</td>
<td>Uosm/Posm = 1</td>
</tr>
<tr>
<td>high U/P creat</td>
<td>low U/P creat</td>
</tr>
<tr>
<td>low U Na (&lt; 10 mmol/l)</td>
<td>U Na &gt; 30 mmol/l</td>
</tr>
<tr>
<td>Low FE Na (&lt; 1%)</td>
<td>High FE Na (&gt; 3 %)</td>
</tr>
<tr>
<td>Low FE ureum &lt; 35%</td>
<td>High FE ureum &gt; 35%</td>
</tr>
</tbody>
</table>

FE Na: U/P Na/ U/P creat
Differential diagnosis between prerenal ARF and acute tubular necrosis

Prevention
Management priorities in ATN (I)

- Search for and correct prerenal and postrenal factors
- Review medications and stop nephrotoxins
- Optimize cardiac output and renal blood flow
- Restore and/or increase urine flow
- Monitor fluid intake and output, daily weight
Potential risk factors for acute Radiocontrast nephropathy

- Pre-existing chronic renal failure
- Diabetes mellitus
- Volume depletion
- Congestive heart failure
- Osmolality of the contrast material
- Dose of contrast material
- Low hematocrit
Differences in nephrotoxicity between Iodixanol and Iohexol in pre-existing diabetic CRF

Incidence of acute radiocontrast-induced renal dysfunction in patients with chronic renal failure according to the presence or absence of DM, therapy with a calcium channel blocker, and attempted prevention with half-isotonic saline alone or in combination with mannitol or furosemide.

Hydration regimens for prevention of contrast media-nephropathy

Impact of hydration in the prevention contrast-induced nephropathy

NaCl 0.9% IV

Unrestricted oral fluid intake

NaCl 0.9% IV

Unrestricted oral fluid intake

Prevention of contrast nephropathy with sodium bicarbonate

Merten et al. JAMA 291:2328-2334, 2004
Influence of acetylcysteine on renal function after radiocontrast exposure

Tepel et al. NEJM 343: 180-184, 2000

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Diagram showing serum creatinine levels before and 48 hours later for control and acetylcysteine groups.
A more recent meta-analysis on acetylcysteine and contrast nephropathy

Effect of acetylcysteine on surrogate markers of renal function in normal volunteers

Prevention of contrast nephropathy with hemofiltration

Contrast-induced nephropathy is a predictor of 1-year mortality

Predictors of 1-year mortality odds ratio (95% CI)

- Hypotension: 3.18 (2.08-4.86)
- Use of intra-aortic balloon pump: 2.49 (1.41-4.41)
- Contrast induced nephropathy: 2.37 (1.63-3.44)
- Diabetes: 1.92 (1.34-2.76)
- Other (peripheral vascular disease, reduced left ventricular function, age)

The basics

This is a whale
Pathophysiology of ATN

• Hemodynamic paradigm
  • Cell fate paradigm
  • Interactive cell biology paradigm
Pathophysiology of ATN

- **Hemodynamic paradigm**
  - vasoconstriction
  - tubular obstruction
  - backleak

- **Cell fate paradigm**
  - loss of cellular polarity
  - necrosis vs apoptosis
  - recovery by growth factors like IGF-1, HGF, EGF

- **Interactive cell biology paradigm**
  - production of inflammatory mediators (TNF, IL)
  - production of cytotoxic agents (superoxide, NO)
  - chemoattraction of neutrophils
Pathophysiology of ATN

- **Hemodynamic paradigm**
  - vasoconstriction
  - tubular obstruction
  - backleak

- **Cell fate paradigm**
  - loss of cellular polarity
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  - recovery by growth factors like IGF-1, HGF, EGF

- **Interactive cell biology paradigm**
  - production of inflammatory mediators (TNF, IL)
  - production of cytotoxic agents (superoxide, NO)
  - chemoattraction of neutrophils
Pathophysiology of ATN

ROLE of ENDOTHELIUM

- Endothelium regulates
  - migration of inflammatory cells
  - vascular tone (and thus perfusion)
  - vasopermeability
  - coagulative properties

- Endothelial dysfunction leads to extension of ARF, which seems to be most expressed in the corticomedullary junction
Effect of graded reduction in renal perfusion pressure on glomerular parameters in volume-deprived rats.

Fluid status in ICU patients
## Classes of fluid balance in ICU

<table>
<thead>
<tr>
<th>DRY-DRY</th>
<th>WET-DRY</th>
<th>DRY-WET</th>
<th>WET-WET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydration</td>
<td>- Cardial insufficiency with dehydration by diuretic therapy and renal hypoperfusion</td>
<td>Third spacing: fluid overload but not in the circulation</td>
<td>Clearly fluid overloaded</td>
</tr>
</tbody>
</table>
Clinical evaluation of intravascular filling status

N=71, non-spontaneous breathing patients

Figure 1. Study design. PLR, passive leg raising; VE, volume expansion.

Monnet et al. Critical Care Medicine. 2006
Clinical evaluation of intravascular filling status

Figure 1. Study design. PLR, passive leg raising; VE, volume expansion.

Figure 4. Receiver operating curves comparing the ability of variations in aortic blood flow (ABF) and pressure (PP) induced by passive leg raising (PLR) (both expressed as percent variation from base 1) to discriminate responders and nonresponders to volume expansion in the whole population.
Invasive radial vs femoral (central) blood pressure

Mignini et al. Critical Care, 2006
Use of Pulmonary artery Catheter

NEJM, 2006, 354, 2213
ARF in sepsis study

• Patient inclusion FIRST day of sepsis criteria
• Patient inclusion only if renal function normal at day 1 of sepsis criteria
• Follow up of renal function after first sepsis criteria

Van Biesen et al, Journal of Nephrology, 2005
Colloid fluid loading (ml)

No-ARF | day | ARF

1 | 2 | 3

321321
Suppression of lung sodium channel and aquaporin 5 expression in acute renal bilateral ischemia/reperfusion

Conservative vs liberal fluid loading in ARDS patients

A prospective, randomized controlled trial based on PAW and/or CVP

P=0.06

P=NS

NEJM 2006, 354, 2564
Conservative vs liberal fluid loading in ARDS patients

**Figure 3.** Probability of Survival to Hospital Discharge and of Breathing without Assistance during the First 60 Days after Randomization.
Kaplan-Meier survival curve in critically ill patients treated with either albumin or saline

Global mortality risk in the « SAFE » study in critically ill patients (albumin vs isotonic saline)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Group</th>
<th>Group</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of deaths/total no.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>726/3473</td>
<td>729/3460</td>
<td>0.99 (0.91–1.09)</td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>81/596</td>
<td>59/590</td>
<td>1.36 (0.99–1.86)</td>
</tr>
<tr>
<td>No</td>
<td>641/2831</td>
<td>666/2830</td>
<td>0.96 (0.88–1.06)</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>185/603</td>
<td>217/615</td>
<td>0.87 (0.74–1.02)</td>
</tr>
<tr>
<td>No</td>
<td>518/2734</td>
<td>492/2720</td>
<td>1.05 (0.94–1.17)</td>
</tr>
<tr>
<td>ARDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24/61</td>
<td>28/66</td>
<td>0.93 (0.61–1.41)</td>
</tr>
<tr>
<td>No</td>
<td>697/3365</td>
<td>697/3354</td>
<td>1.00 (0.91–1.09)</td>
</tr>
</tbody>
</table>

Timing of correction of tissue perfusion on outcome

**Figure 1**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample Size</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone et al.</td>
<td>(n = 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuchschmidt et al.</td>
<td>(n = 51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gutierrez et al.</td>
<td>(n = 119)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yu et al.</td>
<td>(n = 67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hayes et al.</td>
<td>(n = 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yu et al.</td>
<td>(n = 88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gattinoni et al.</td>
<td>(n = 762)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Odds ratio and 95% confidence interval for studies (total of 1031 patients) attempting to improve tissue perfusion after onset of tissue hypoxic can be expected. No beneficial effect on mortality was seen. (Modified from [30].)

**Figure 2**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample Size</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schultz et al.</td>
<td>(n = 85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoemaker et al.</td>
<td>(n = 58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berlauk et al.</td>
<td>(n = 89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fleming et al.</td>
<td>(n = 67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gutierrez et al.</td>
<td>(n = 141)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boyd et al.</td>
<td>(n = 107)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bishop et al.</td>
<td>(n = 115)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Odds ratio and 95% confidence interval for studies (total of 662 patients) attempting to improve tissue perfusion before onset of tissue hypoxic can be expected. Beneficial effect on mortality were seen. (Modified from [30].)
Figure 4. Variables of renal function as mean arterial pressure (MAP) was increased from 65 to 85 mm Hg. No significant changes were observed when MAP was increased. Open bars, group 1, MAP 65 mm Hg; filled bars, group 2, MAP 85 mm Hg (mean ± sd).

Impact of MAP 65mmHg or 85mmHg

Bourgoin et al, Crit Care, 2005
Increasing MAP to supraphysiologic levels is not efficient to increase oxygen delivery. This is reasonable in virgin cardiovascular patients.

Bourgoin et al, Crit Care, 2005
Effect of norepinephrine on diuresis in septic shock patients

Martin et al Chest 103:1826-1831, 1993
Survival of septic shock patients treated with vasopressors

Use of dopamine in ARF: a meta-analysis

Plot showing relative risks (diamonds) and 95% confidence intervals (lines) for all studies and for subgroups A, B, and C.

A: excluding studies using contrast
B: Studies limited to heart disease
C: excluded statistical outliers

Kellum and Decker Crit Care Med
29:1526-1531, 2001
Vasopressin in shock

Vasopressin:
- strong splanchnic vasoconstriction
- Eferent glomerular vasoconstriction
- Deficient in many shock patients

Tsuneyoshi et al, Crit Care Med, 2001
Figure 3. Urine output measured during the course of the 16-hr vasopressin infusion. **p < .05 compared with baseline (0 hrs).

Tsuneyoshi et al, Crit Care Med, 2001
Vasopressin 1IU/hour and hepatorenal syndrome

Eisenmann, J Int Med, 1999
Vasopressin 1IU/hour and hepatorenal syndrome

± 2423 mL 24 \(^{-1}\)h (\(P = 0.0012\)), respectively. The improvement in urine output was not accompanied by a parallel improvement in creatinine clearance. The overall outcome did not change, and all patients except two in each group succumbed to their end-stage disease, due to nonrenal causes.
Non-dialytic therapeutic interventions in ARF

- **Volume therapy:**
  - crystalloids; colloids
- **Vasopressors:**
  - Norepinephrine, dopamine, dobutamine
- **Diuretics:**
  - Mannitol; *loop diuretics*
- **Renal vasodilators:**
  - Natriuretic peptides; *Ca antagonists*
- **Free radical scavengers:**
  - Acetylcysteine
- **Growth factors:**
  - IGF-1
- **Tight metabolic control:**
  - Glucose, insulin
Loop diuretics in ARF: a double-blind randomized controlled trial

## Effect of diuretics on Mortality and Nonrecovery of renal function

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted OR (95% CI)</th>
<th>Covariate adjusted OR (95% CI)</th>
<th>Covariate and propensity score adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In-hospital mortality</strong></td>
<td>1.37 (0.97-1.92)</td>
<td>1.65 (1.05- 2.58)</td>
<td>1.68 (1.06-2.64)</td>
</tr>
<tr>
<td><strong>Nonrecovery of renal function</strong></td>
<td>1.53 (1.08-2.15)</td>
<td>1.70 (1.14-2.53)</td>
<td>1.79 (1.19-2.68)</td>
</tr>
<tr>
<td><strong>Death or nonrecovery</strong></td>
<td>1.48 (1.02-2.12)</td>
<td>1.74 (1.12-2.68)</td>
<td>1.77 (1.14-2.76)</td>
</tr>
</tbody>
</table>

Mehta et al JAMA 288: 2547-2553, 2002
Database analysis of the effect of diuretics on mortality in patients with ARF

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>No Diuretics</th>
<th>Diuretics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of ICU stay, days</td>
<td>10 (5–22)</td>
<td>9 (4–20)</td>
<td>11 (5–22)</td>
</tr>
<tr>
<td>Length of hospital stay, days</td>
<td>22 (11–44)</td>
<td>21 (9–44)</td>
<td>23 (12–45)</td>
</tr>
<tr>
<td>ICU mortality, %</td>
<td>51.6</td>
<td>48.2</td>
<td>53.4</td>
</tr>
<tr>
<td>Hospital mortality, %</td>
<td>60.5</td>
<td>57.1</td>
<td>62.4</td>
</tr>
<tr>
<td>Hospital discharge without RRT, %</td>
<td>34.7</td>
<td>38.2</td>
<td>32.7</td>
</tr>
<tr>
<td>Hospital discharge with RRT, %</td>
<td>4.8</td>
<td>4.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Number of patients</td>
<td>1743</td>
<td>626</td>
<td>1117</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range) or percentage.

Effect of control of mean blood glucose in ICU patients

Percentage of risk for several complications in ICU patients with stay > 5 days

Cumulative risk of hospital death in ICU patients with stay > 5 days

21-Day Dialysis-Free Survivorship.

All subjects (n=504)

Oliguric (n=121)

Non-oliguric (n=376)

* p=0.005 A vs. P

Lewis et al, AJKD 2000
21-Day Survivorship.

- Placebo
- Anaritide (atrial natriuretic peptide)

* p=0.005 A vs. P

Sward et al, Crit Care Med, 2004
Whom to believe?

• Patient population: all ICU vs only Cardiosurgery
• Only patients with limited renal dysfunction included (exclusion if oliguria, aminoglycosides, abdominal aorta surgery etc)
• Dose: 200ng/kg/min vs 50ng/kg/min: 94% vs 45% of the patients suffered hypotension
• Duration: only 24 hours vs until endpoint
Whom to believe?

- Patient population: all ICU vs only Cardiosurgery
- Only patients with limited renal dysfunction included (exclusion if oliguria, aminoglycosides, abdominal aorta surgery etc)
- Dose: 200ng/kg/min vs 50ng/kg/min: 94% vs 45% of the patients suffered hypotension
- Duration: only 24 hours vs until endpoint

Joke: To maintain a healthy body, you must drink at least 8-10 glasses of water per day.
Whom to believe?

- Patient population: all ICU vs only Cardiosurgery
- Only patients with limited renal dysfunction included (exclusion if oliguria,

Only effective in initiation phase/extension phase

- Dose: 200ng/Kg/min vs 50ng/Kg/min: 94% vs 45% of the patients suffered hypotension
- Duration: only 24 hours vs until endpoint
Ischemia–reperfusion results in reversible or irreversible injury to the proximal tubular cell (J Bonventre)
If a lot of cures are suggested for a disease, it usually means that the disease is incurable

Anton Chekhov in The Cherry Orchard
CRRT vs IHD

Ghent University hospital 1995-1999 (N=557)

% survival

Apache-score

* p<0.05
** p <0.01
*** p<0.001
Survival IHD vs CRRT

Simpson
Kierdorf
Sandy
Johns
Mehta
Uehlinger
Total

Relative risk (IHD) 0.2 0.5 1 2 10

Tonelli et al, AJKD, 40, 875-885, 2002
Survival IHD vs CRRT
A randomised controlled trial

<table>
<thead>
<tr>
<th></th>
<th>Intermittent haemodialysis</th>
<th>Continuous venovenous haemodiafiltration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of sessions (h)</td>
<td>5.2 (5.1–5.3)</td>
<td>continuous</td>
</tr>
<tr>
<td>Blood flow (mL per min)</td>
<td>278 (275–281)</td>
<td>146 (145–147)</td>
</tr>
<tr>
<td>Dialysate flow*</td>
<td>500</td>
<td>1099 (1068–1128)</td>
</tr>
<tr>
<td>Ultrafiltration flow (mL per h)</td>
<td>1278 (1255–1301)</td>
<td></td>
</tr>
<tr>
<td>Net ultrafiltration† (mL per day)</td>
<td>2213 (2141–2285)</td>
<td>2107 (2011–2203)</td>
</tr>
<tr>
<td>Mean urea (mmol/L)</td>
<td>15.7 (7.5)</td>
<td>14.8 (9.1)</td>
</tr>
</tbody>
</table>

Data are mean (95% CI) or mean (SD). *mL per min in the intermittent haemodialysis group and mL per h in the continuous venovenous haemodiafiltration group. †Mean volume loss per day of treatment.

Table 2: Treatment modalities

Vinsonneau et al, Lancet 2006, Hemodaife
### Survival IHD vs CRRT

#### A randomised controlled trial

Vinsonneau et al, Lancet 2006, Hemodaife

<table>
<thead>
<tr>
<th></th>
<th>Intermittent haemodialysis</th>
<th>Continuous venovenous haemodiafiltration</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Survival</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 28</td>
<td>41.8% (34.7–49.0)</td>
<td>38.9% (31.6–46.1)</td>
<td>0.65</td>
</tr>
<tr>
<td>Day 60 (primary endpoint)</td>
<td>31.5% (24.8–38.2)</td>
<td>32.6% (25.6–39.5)</td>
<td>0.98</td>
</tr>
<tr>
<td>Day 90</td>
<td>27.2% (20.8–33.6)</td>
<td>28.5% (21.8–35.2)</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>Renal support duration (days)</strong></td>
<td>11 (8–13)</td>
<td>11 (8–14)</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Length of ICU stay (days)</strong></td>
<td>20 (16–23)</td>
<td>19 (15–22)</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>Length of hospital stay (days)</strong></td>
<td>30 (24–35)</td>
<td>32 (22–42)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Values are mean (95% CI). ICU-intensive-care unit.

*Table 3: Outcomes according to treatment group*
Survival IHD vs CRRT
A randomised controlled trial

Vinsonneau et al, Lancet 2006, Hemodiaife
**Survival IHD vs CRRT**  
**A randomised controlled trial**

<table>
<thead>
<tr>
<th></th>
<th>Intermittent haemodialysis (n=184)</th>
<th>Continuous venovenous haemofiltration (n=175)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension*</td>
<td>72 (39%)</td>
<td>61 (35%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Bleeding event†</td>
<td>13 (7%)</td>
<td>12 (7%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>22 (12%)</td>
<td>31 (18%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>12 (7%)</td>
<td>7 (4%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Hypophosphataemia</td>
<td>13 (7%)</td>
<td>14 (8%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>10 (5%)</td>
<td>31 (17%)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>18 (10%)</td>
<td>9 (5%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Catheter infection</td>
<td>2 (1%)</td>
<td>3 (2%)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Data are number (percentage). *All hypertensive episodes were recorded from initiation until end of renal replacement therapy. Hypotension means at least one hypertensive episode during follow-up. †Bleeding events were reported only when transfusion was needed.

**Table 4: Adverse events according to treatment group**

Vinsonneau et al, Lancet 2006, Hemodaife
CRRT: Disadvantages

- Inconvenience
- Cost
- Bleeding
- Fluid balance errors
- Electrolyte disorders
- Hypothermia
Comparison of continuous and intermittent renal replacement therapy for acute renal failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter</th>
<th>n</th>
<th>% mortality</th>
<th>OR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRT group</td>
<td>CVVHDF</td>
<td>70</td>
<td>47.1%</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>IHD</td>
<td>55</td>
<td>50.9%</td>
<td>1.16</td>
<td>0.36</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>86</td>
<td>45.3%</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>39</td>
<td>53.8%</td>
<td>1.41</td>
<td>0.39</td>
</tr>
<tr>
<td>Pre-existing CRF</td>
<td>No</td>
<td>98</td>
<td>44.9%</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>27</td>
<td>63.0%</td>
<td>2.09</td>
<td>0.45</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;60</td>
<td>40</td>
<td>47.5%</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>60–70</td>
<td>41</td>
<td>51.2%</td>
<td>1.16</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>&gt;70</td>
<td>44</td>
<td>45.5%</td>
<td>0.92</td>
<td>1.00</td>
</tr>
</tbody>
</table>

No difference regarding:
- Hospital / ICU length of stay
- Duration of RRT

NADA difference in survival (p=0.36)

CRRT vs IHD a randomised controlled trial

191 ICU patients with ARF requiring RRT

129 patients randomized (Biased coin randomization)

62 patients not randomized (non medical reasons)

125 patients correctly randomized

4 patients with violation of the randomization protocol

70 patients CVVHDF

55 patients IHD
## CRRT: Disadvantages

<table>
<thead>
<tr>
<th>Cost (US$)/day</th>
<th>CVVH</th>
<th>CVVHD</th>
<th>CVVHDF</th>
<th>IHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No antico</td>
<td>564</td>
<td>601</td>
<td>592</td>
<td>344</td>
</tr>
<tr>
<td>Heparin</td>
<td>498</td>
<td>526</td>
<td>527</td>
<td></td>
</tr>
<tr>
<td>Citrate</td>
<td>NA</td>
<td>NA</td>
<td>731</td>
<td></td>
</tr>
</tbody>
</table>

Total (not including nursing costs)

(including nursing costs)

Effects of different doses of UF on outcome of ARF in critically ill patients.

Potential Sites of Volume Application in the Extracorporeal Circuit

- Blood from the patient
- Substitution solution (predilution)
- Ultrafiltrate (+ dialysis fluid)
- Substitution solution (postdilution)
- Dialysis fluid
- Blood back to the patient
Postdilution-CVVH

- CVVH: continuous veno-venous haemofiltration
- Postdilution: substitution fluid is infused after the filter
- haemoconcentration limits possible exchange volume (up to 20% of the blood flow are optimal)
- toxins are not diluted before ultrafiltration
- most effective use of substitution solution
Predilution-CVVH

- CVVH: continuous veno-venous haemofiltration
- Predilution: substitution solution is infused before the filter
- no haemoconcentration
- with the same volume of haemofiltration solution less effective than other set-ups
Urea Clearance with different set-ups

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

- HF: 2 l/h substitution solution
- HDF: 1 l/h dialysis fluid, 1 l/h substitution solution, \( Q_B = 100 \) ml/min
- theoretical limit: 2000 ml/h = 33,3 ml/min
- post-dilution is more effective than pre-dilution

Effects of bicarbonate- and lactate-buffered replacement fluids on cardiovascular outcome in CVVH patients

Michael Barenbrock, Martin Hausberg, Fritz Matzkies, Stephan de la Motte, and Roland M. Schaefer

Department of Medicine D, University of Münster, Münster, and Statistical Institute, Harrison Clinical Research, Munich, Germany

- Randomised, multicentric
- 117 patients with CVVH
- Better control of acidosis with bicarbonate
- less cardiovascular complications

Kidney Int. 2000; 58: 1751-57
“Classic IHD” 4 hours 3 times/week

“Slow (adaptable and daily) hemodiafiltration”

CVVHD high volume

“Classic CRRT”

CVVHD
CVVH
CAVHD
CAVH
Table 1 | Treatment parameters for current and previous SLED studies

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Kumar et al.⁴</th>
<th>Marshall et al.⁵</th>
<th>Marshall et al.⁶</th>
<th>This study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment name</td>
<td>EDD</td>
<td>SLED</td>
<td>SLEDD-f</td>
<td>SLED</td>
</tr>
<tr>
<td>Hours/day</td>
<td>7.5</td>
<td>12</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Days/week</td>
<td>6–7</td>
<td>6–7</td>
<td>4–7</td>
<td>6</td>
</tr>
<tr>
<td>Blood pump speed (ml/min)</td>
<td>200</td>
<td>100</td>
<td>300</td>
<td>200</td>
</tr>
<tr>
<td>Dialysate flow (ml/min)</td>
<td>300</td>
<td>200</td>
<td>200</td>
<td>350</td>
</tr>
<tr>
<td>Replacement fluid (ml/min)</td>
<td>—</td>
<td>—</td>
<td>100</td>
<td>17</td>
</tr>
</tbody>
</table>

EDD, extended daily dialysis; SLED, sustained low-efficiency dialysis; SLEDD-f, sustained low-efficiency daily dialfiltration.
The Genius dialysis System.
SLEDD: hemodynamic stability

Kumar et al, AJKD, 36, 294-300, 2000
## SLEDD: Adequacy

<table>
<thead>
<tr>
<th></th>
<th>SLEDD</th>
<th>CRRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow (ml/min)</td>
<td>100-300</td>
<td>100-200</td>
</tr>
<tr>
<td>Dialysate flow (ml/min)</td>
<td>100</td>
<td>15-35</td>
</tr>
<tr>
<td>Daily urea clearance (l)</td>
<td>80-90</td>
<td>20-40</td>
</tr>
<tr>
<td>Daily Kt/V</td>
<td>2,4</td>
<td>0,9-1,4</td>
</tr>
<tr>
<td>Daily dialysate cost (US$)</td>
<td>10</td>
<td>50-100</td>
</tr>
</tbody>
</table>

Schlaefer et al, KI, 56, suppl 7, S20-S23
CRRT vs IHD a randomised controlled trial

Uelingher et al

- Average daily duration of RRT (h)
- Urea clearance during RRT (ml/min)
- Average daily urea clearance (ml/min)

P < 0.0001
SLEDD and solute removal

Van Biesen et al, submitted
SLEDD and solute removal

Van Biesen et al, submitted
SLEDD and solute removal

Van Biesen et al, submitted
SLEDD: anticoagulation

No heparin: 31.9% in SLEDD vs 2.7% in CCVH (p<0.05)

Kumar et al, AJKD, 36, 294-300, 2000
Anticoagulation in Genius

- Citrate is an ideal local anticoagulant
- However, in hemofiltration, there is a risk for accumulation of citrate and/or metabolic alkalosis, as citrate is not filtered out.
- In Genius, citrate is completely dialysed out when given pre-filter
  - Morgera protocol: 4% trisodium citrate prefilter at 180ml/hour for a Qb of 200ml; dialysate Calcium 1.00mmol/l
  - University Ghent protocol: 30% trisodium citrate, at 25ml/hour for a Qb of 250; dialysate calcium 1.25mmol/l

For both: check Blood Calcium after 15’: aim at around 0.7mmol
<table>
<thead>
<tr>
<th></th>
<th>SLED ($)</th>
<th>CRRT citrate ($)</th>
<th>CRRT heparin ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supply cost/day</td>
<td>69.75</td>
<td>402.80</td>
<td>334.95</td>
</tr>
<tr>
<td>HD RN cost/day</td>
<td>168.75(^a)</td>
<td>37.50</td>
<td>37.50</td>
</tr>
<tr>
<td>Total cost/day</td>
<td>238.50</td>
<td>440.30</td>
<td>372.45</td>
</tr>
<tr>
<td>Total cost/week</td>
<td>1431</td>
<td>3089</td>
<td>2607</td>
</tr>
</tbody>
</table>

CRRT, continuous renal replacement therapy; HD, hemodialysis; RN, registered nurse; SLED, sustained low-efficiency dialysis.

\(^a\)Note: Based on one HD nurse treating two patients.
## Table 4 | Measures of small solute removal

<table>
<thead>
<tr>
<th></th>
<th>CRRT</th>
<th>SLED</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning serum creatinine after day 3 (μmol/l)</td>
<td>136 ± 49</td>
<td>120 ± 55</td>
<td>0.06</td>
</tr>
<tr>
<td>Time-averaged serum creatinine (μmol/l)</td>
<td>136 ± 49</td>
<td>95 ± 49</td>
<td>0.03</td>
</tr>
<tr>
<td>Weekly $K_t/V$</td>
<td>7.1 ± 2.1</td>
<td>8.4 ± 1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EKR$_j$ (ml/min)</td>
<td>31 ± 10</td>
<td>31 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>EKR$_{jc}$ (ml/min)</td>
<td>28 ± 9</td>
<td>29 ± 6</td>
<td>NS</td>
</tr>
</tbody>
</table>

CRRT, continuous renal replacement therapy; NS, not significant; SLED, sustained low-efficiency dialysis.
Conclusions:
Lessons to be learned
Conclusions: Lessons to be learned

1) Use correct terminology: Reporting of AKI as by RIFLE criteria
Conclusions: Lessons to be learned

2) Early recognition of renal failure is of importance: too late is too late....
Conclusions:
Lessons to be learned

3) Pressure might be more important than water, that might even be dangerous
Conclusions:
Lessons to be learned

4) Although we know a lot about ARF, still there is more we do not know....