Rationale for renal replacement therapy in ICU: indications, approaches and outcomes

Richard Beale
RIFLE classification (ADQI group) 2004

- **Risk**: Abrupt (1–7) days decrease (>25% in GFR, or serum creatinine × 1.5 sustained)
- **Injury**: Adjust creatinine or GFR decrease > 50% serum creatinine × 2
- **Failure**: Adjust creatinine or GFR decrease > 75% serum creatinine × 3 or serum creatinine > 4 mg% when acute increase > 0.5 mg%
- **Loss**: Irreversible AKI or persistent AKI > 4 weeks
- **Outcome**: ESRD > 3 months

- **Non-oliguria**
  - Decreased UO relative to fluid input
  - UO < 0.5 mg/kg/h × 6 h

- **Oliguria**
  - UO < 0.5 mg/kg/h × 12 h
  - UO < 0.5 mg/kg/h × 12 h? Anuria × 12 h

- **Specificity**
  - AKI - earliest time point for provision of RRT
### AKIN classification

**Definition:** Abrupt *(within 48 hrs)* change in serum creatinine or urine output (after exclusion of obstruction)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Creatinine criteria</th>
<th>Urine output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>↑ serum creatinine of $\geq 0.3$ mg/dl (26.4 μmol/L) or 1.5–2 fold increase from baseline</td>
<td>&lt;0.5ml/kg/hr for $&gt;6$ hr</td>
</tr>
<tr>
<td>2</td>
<td>2–3 fold rise of serum creatinine from baseline</td>
<td>&lt;0.5ml/kg/hr for $&gt;12$ hrs</td>
</tr>
<tr>
<td>3</td>
<td>$&gt;3$ fold rise of serum creatinine from baseline</td>
<td>&lt;0.3ml/kg/hr $\times 24$ hr or anuria $\times 12$ hr</td>
</tr>
<tr>
<td></td>
<td>or serum creatinine $\geq 4.0$ mg/dl (&gt;354 μmol/L) with an acute rise of at least 0.5 mg/dl (44 umol/L)</td>
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<tr>
<td></td>
<td>or treatment with RRT</td>
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</tbody>
</table>

KDIGO classification

Aim:
To harmonise RIFLE and AKIN criteria and to agree on ONE universal definition
We recommend that AKI be defined as any of the following (1A):

- Increase in Scr by $>0.3$ mg/dl ($>26.4$ µmol/L) within 48 hours,
  or
- Increase in Scr by $>1.5$-fold above baseline which is known or presumed to have occurred within 7 days
  or
- Urine volume $<0.5$ ml/kg/h for 6 hours.
KDIGO classification
Staging

If criteria for AKI met, we recommend to stage AKI as:

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<tr>
<td>1</td>
<td>≥ 1.5-1.9 times baseline or 0.3 mg/dl (&gt;26.4 µmol/L) increase</td>
<td>&lt; 0.5 ml/kg.h for ≥ 6-12 hrs</td>
</tr>
<tr>
<td>2</td>
<td>≥ 2.0-2.9 times baseline</td>
<td>&lt; 0.5 ml/kg.h for ≥ 12 hrs</td>
</tr>
<tr>
<td>3</td>
<td>≥ 3.0 times baseline OR increase in creatinine ≥ 4 mg/dl (352 µmol/L) OR Anuria ≥ 12 hrs</td>
<td>&lt; 0.3 ml/kg.h for ≥ 24 hrs OR Anuria ≥ 12 hrs</td>
</tr>
<tr>
<td></td>
<td>In patients &lt; 18 yrs decrease of eGFR to 35 ml/kg/1.73 m²</td>
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</tbody>
</table>
RRT in AKI: Why?
RRT in AKI: Why?

Aims of RRT

✓ Amelioration of uraemia and fluid overload
✓ Metabolic homeostasis
✓ Volume homeostasis (ie. ARDS, CCF, MOF)

? Immunomodulation in sepsis

Replacement of renal function + organ support
Types of RRT in AKI

**CRRT**
- continuous veno-venous haemofiltration
- continuous haemodialysis
- continuous veno-venous haemodiafiltration (peritoneal dialysis)

**Intermittent RRT**
- intermittent haemodialysis
- Slow Extended Dialysis (SLED)
- Prolonged intermittent RRT (PIRRT)
- SLED-F
No evidence that CRRT is superior (patient survival, renal recovery)

Aim: to identify optimal mode for individual patient

haemodynamic instability
severe fluid overload
brain oedema
liver failure

recovery phase
able to tolerate fluid swings

CRRT or intermittent RRT?

Advantages and disadvantages of both techniques

CRRT

IHD / SLED / PIRRT
Modality

- **IHD**
- **SLED PIRRT**
- **PD**
- **CRRT**

**Clearance per hour**
- IHD: +++
- SLED PIRRT: ++
- PD: +
- CRRT: +

**Fluid shifts**

**Changes in urea/NH$_3$/Na$^+$**
RRT in AKI: When?
Optimal timing of RRT

<table>
<thead>
<tr>
<th>Early RRT</th>
<th>Late RRT</th>
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</thead>
<tbody>
<tr>
<td>Metabolic homeostasis</td>
<td>Avoids RRT in patients whose renal function recovers without RRT</td>
</tr>
<tr>
<td>Fluid management “easier”</td>
<td>Avoids potential complications of central line</td>
</tr>
<tr>
<td></td>
<td>Cost saving</td>
</tr>
<tr>
<td></td>
<td>Risk of uraemic complications</td>
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</tbody>
</table>
Optimal timing of RRT

No accepted definition of “optimal timing of RRT” and wide variation in clinical practice

Variable interpretation of “optimal timing”:

? specific urea level
? specific creatinine level
? time since development of AKI
? time since admission to ICU
? time since admission to hospital
Only 2 published RCTs (and 2 RCTs in abstract form) and at least 15 observational studies comparing

“early” vs “late” RRT
Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: A prospective, randomized trial

Catherine S. C. Bouman, MD; Heleen M. Oudemans-van Straaten, MD, PhD; Jan G. P. Tijssen, MD, PhD; Durk F. Zandstra, MD, PhD; Jozef Kesecioglu, MD, PhD

Crit Care Med 2002;30(10)

106 patients (3-organ failure, oliguric AKI)
1998 – 2000; 2-centre study

Randomisation:
- early high-volume CVVH (72-96 L/24 hrs)
- vs early low-volume CVVH (24-36 L/24 hrs)
- vs late low-volume CVVH (24-36 L/24 hrs)
Optimal timing of RRT

Results:
No difference in 28-day survival
No difference in renal recovery

In the late low volume group:
2 patients died before criteria were met for late CVVH
4 patients had spontaneous recovery of renal function
Optimal timing of RRT

“Early start on continuous hemodialysis therapy improves survival rate in patients with acute renal failure following coronary bypass surgery”

28 patients post cardiac surgery

CRRT if urine output <30ml/h for 3 hours vs CRRT if urine output <20ml/h for 2 hours

Results: 14 day mortality
14% (early CRRT)
86% (late CRRT)

Sugahara S et al. Hemodial Int 2004:8:320
Optimal timing of RRT

15 additional observational mainly retrospective studies
### Early versus late RRT

<table>
<thead>
<tr>
<th>First Author</th>
<th>Time period</th>
<th>RRT mode</th>
<th>n</th>
<th>Urea</th>
<th>Hospital mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gettings</td>
<td>1989 - 1997</td>
<td>CAVHD</td>
<td>100 trauma pts</td>
<td>&lt;21 Day 10</td>
<td>61% vs 80%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CVVHD</td>
<td></td>
<td>≥21 Day 19</td>
<td></td>
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<td></td>
<td></td>
<td>CVVH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tsai</td>
<td>2002 - 2005</td>
<td>CVVH</td>
<td>98 post abdo Sx</td>
<td>23</td>
<td>43% vs 75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IHD</td>
<td></td>
<td>27</td>
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</tr>
<tr>
<td>Liu (PICARD)</td>
<td>1999 - 2001</td>
<td>CRRT</td>
<td>243 mixed pts</td>
<td>&lt;27</td>
<td>RR 1.85 with</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IHD</td>
<td></td>
<td>≥27</td>
<td>higher urea</td>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥27</td>
<td></td>
</tr>
<tr>
<td>Bagshaw (BEST)</td>
<td>2000 - 2001</td>
<td>CRRT, IHD</td>
<td>1260 mixed pts</td>
<td>≤24</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;24</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>≤309</td>
<td>71% vs 53.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;309</td>
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</table>
Optimal timing of RRT

15 observational studies:

Most evidence in favour of “early” RRT stems from small retrospective observational studies.

But:

• inclusion of patients with AKI who would have recovered renal function anyway
• inclusion of patients into “late arm” who received RRT “too late”
• differences in severity of illness between groups
## Parameters affecting mortality

<table>
<thead>
<tr>
<th>Parameter at time of RRT</th>
<th>OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum pH</td>
<td>0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVS failure</td>
<td>1.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Urine output &lt;400</td>
<td>1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>1.62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haematological failure</td>
<td>1.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pre-existing advanced chronic illnesses</td>
<td>1.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Need for TPN</td>
<td>2.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Liver failure</td>
<td>2.44</td>
<td>0.001</td>
</tr>
<tr>
<td>Ventilated</td>
<td>6.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>0.999</td>
<td></td>
</tr>
<tr>
<td>Serum Urea</td>
<td>1.004</td>
<td></td>
</tr>
</tbody>
</table>

Ostermann et al, Crit Care 2009
Impact of fluid overload

“Fluid accumulation, survival and recovery of kidney function in critically ill patients with AKI”

PICARD study:
Observational study in 5 centres in California
1999 – 2001

618 patients with AKI
of whom 398 patients received RRT (CVVH, CVVHD or IHD)

Fluid status defined as change from initial hospital admission weight.

Bouchard et al, KI 2009;76
Impact of fluid overload

Mortality rate of RRT patients by final fluid accumulation relative to baseline weight

ICU mortality (%) vs. % weight change from baseline.
RRT in AKI: When?
RRT in AKI: When?

**AKI**

- Presence of life-threatening complications of AKI which cannot be reversed quickly by simple means?
  - **No**
  - **Yes** → **Start RRT (if appropriate)**

  **Optimise haemodynamics:**
  - ensure adequate intravascular volume repletion
  - correct hypotension, aim for MAP ≥ 65mmHg
  - Discontinue nephrotoxic drugs if possible

- Regular assessment of volume status, non-renal organ dysfunction, severity of illness and AKI trends

  **Persistent AKI and any of the following?**
  - Urine output ≤500-600ml/24
  - Progressive acidosis
  - Progressive fluid accumulation
  - Worsening non-renal organ dysfunction
  - Worsening pulmonary oedema

  - **No**
  - **Yes** → **Consider RRT**

Ostermann M et al. NDT 2012
RRT in AKI: How much?
Dose of RRT

Traditional approach in ESRD: Kt/V

Kt/V not validated in AKI (lack of steady state, fluid shifts)

Measures of dose in RRT

1. Filtrate volume
2. Frequency of intermittent RRT
Optimal dose of RRT

“Effects of different doses in CVVH on outcomes of acute renal failure: a prospective randomised trial”

425 ICU patients with AKI

1994 – 1999

Protocol: Group I: UF 20 ml/kg/hr
Group II: UF 35 ml/kg/hr
Group III: UF 45 ml/kg/hr

Ronco et al, Lancet 2000;356
Effects of different doses of UF on outcome of ARF in critically ill patients.

Optimal dose of RRT
Optimal dose of RRT

1124 ICU patients with AKI and ≥1 non-renal organ failure or sepsis

If haemodynamically stable: intermittent haemodialysis
3x / week or 6x / week

If haemodynamically unstable:
   CVVHDF or SLED
   20 ml/kg/hr vs 35 ml/kg/hr
   3x/wk vs 6x/wk

Primary endpoint: 60 day mortality
Conclusions:
Intensive renal support in critically ill patients with AKI did not decrease mortality
not improve recovery of kidney function
not reduce the rate of non-renal organ failure

The VA/NIH Acute Renal Failure Trial Network. NEJM 2008;359
Optimal dose of RRT

Criticisms

1. No agreed criteria when to start RRT
2. Combined use of intermittent and continuous RRT
3. Modality switches within each treatment arm
4. Option of isolated ultrafiltration for volume management on non-dialysis days
5. Fixed dose of RRT throughout the dynamic course of AKI
Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients

The RENAL Replacement Therapy Study Investigators*
Optimal dose of RRT

1508 ICU patients with AKI

RCT: CVVHDF

40 ml/kg/hr vs 25 ml/kg/hr

(n=747)  (n=761)
Conclusion:
Treatment with high dose RRT did not reduce 90 day mortality

RENAL study. NEJM 2009;361
Dose of RRT

Intensity of Renal Support in Critically Ill Patients with Acute Kidney Injury
The VA/NHL Acute Renal Failure Trial Network

Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients
The RENAL Replacement Therapy Study Investigators
High dose RRT in sepsis / septic shock?
CRRT in sepsis

Anti-inflammatory cytokines vs. Pro-inflammatory cytokines

KDa

100
80
60
40
20

IL6 SR
IL4
IL1 SR
IL10

IL6 SR
IL4
IL1 SR
IL10

Endotoxin
IL12
PAI-1
IL6
CRP
TNFα
Kinins
PAF

Membrane cut-off points

Polysulfone 30kDa
Polyamide 30kDa
AN69 50kDa
Polyamide100 100kDa
High dose RRT in sepsis / septic shock?

**IVOIRE** trial  (HIgh VOlume in Intensive CaRE trial)

RCT: CVVH 70m/kg/hr  vs  CVVH 35ml/kg/hr  
for 96 hrs

Planned study size: 460
Stopped in October 2010 after enrolment of 140 patients

Preliminary results:
No difference in 28 day mortality
Optimal dose of RRT
Optimal dose of RRT

RRT Dose and Survival

Survival

Dose Dependent

Break Point

Dose Independent

RRT Dose
Dose of RRT in daily clinical practice

“Delivered dose of renal replacement therapy and mortality in critically ill patients with AKI”

prospective multicenter observational study (8 countries)

419 pts on CRRT and 88 pts on intermittent RRT

Results:

• 20% of pts on CRRT had ≥1 interruption of 18hrs
• delivered dose of RRT often lower than intended as a result of treatment interruptions

Vesconi S et al. Crit Care 2009;13
Reasons for treatment interruptions
- circuit clotting
- diagnostic and therapeutic procedures
- catheter malfunction

Vesconi S et al. Crit Care 2009;13
RRT in AKI: how much?

Consensus:

• There is no benefit in increasing the dose of RRT beyond a sufficient dose (~ 25ml/kg/hr)

• But: “Underdialysis” of critically ill patients must be avoided.

• Need for regular review and adjustment of RRT dose.

• Lack of data for flexible dosing (ie higher dose during acute phase)
Conclusions

**Dialysis or CRRT?**
No evidence that CRRT is superior to haemodialysis in AKI in most patients
But need for individualised treatment

**Why?**
to maintain homeostasis
to provide replacement of renal function and organ support

**When?**
AKI and progressive fluid accumulation, non-renal organ failure or metabolic acidosis, independent of creatinine

**How much?**
No evidence that “more” RRT is better than “enough”.
Consensus that 25ml/kg/hr adequate in most situations but undertreatment must be avoided
Need to review dose on regular basis and adjust Rx