Timing of renal replacement therapy initiation in acute kidney injury

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Objectives

1- Review current practice and attitudes around the timing of RRT initiation in AKI

2- Review the benefits and limitations of earlier initiation of RRT in AKI

3- Present future directions around study of RRT timing in AKI
The KDIGO AKI Guidelines

• 5.1.1: Initiate RRT emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist. (Not Graded)

• 5.1.2: 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)
Indications for the initiation of renal replacement therapy in AKI

• Classic indications
  – hyperkalemia
  – severe metabolic acidosis
  – volume overload
  – oligoanuria
  – uremic complications
  – drug intoxications

• Potential indications
  – hemodynamic instability
  – catabolic states
  – sepsis
  – increased ICP
What triggers the initiation of RRT in Canada: Survey data

• hyperkalemia and volume overload are widely utilized triggers
• even when there was consensus around starting RRT, there was no uniformity regarding rationale
• non-clinical factors play an important role as well (eg, time of the day, day of the week)

Clark et al NDT 2012
An international perspective

• 172 nephrologists responded
• severity of illness, potassium and oxygenation were key driving factors in decision to start RRT
• 53% of respondents felt that there was no evidence to start RRT “early”
• 46% practice “early” RRT initiation

BOTTOM LINE: NO STANDARD OF CARE EXISTS

Thakar et al Crit Care 2012
Plausible reasons to support earlier initiation of RRT

- improved volume control
- quicker restoration of acid-base homeostasis
- accelerated removal of small and middle-sized molecules
- avoidance of morbidity associated with “wait for a complication” approach to initiation of RRT
Kidney Attack

John A. Kellum, MD
Rinaldo Bellomo, MD
Claudio Ronco, MD
The case for earlier initiation of RRT in AKI

OR for 28-day mortality 0.45 (95% CI, 0.28-0.72)

Karvellas et al Crit Care 2011
The case for earlier RRT: ATN vs RENAL

<table>
<thead>
<tr>
<th></th>
<th>ATN</th>
<th>RENAL</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>59</td>
<td>65</td>
</tr>
<tr>
<td>SOFA</td>
<td>7.6</td>
<td>7.6</td>
</tr>
<tr>
<td>Mechanically ventilated</td>
<td>80%</td>
<td>75%</td>
</tr>
<tr>
<td>Mortality</td>
<td>52% (Day 60)</td>
<td>45% (Day 90)</td>
</tr>
<tr>
<td>RRT dependence</td>
<td>24% (Day 60)</td>
<td>6% (Day 90)</td>
</tr>
<tr>
<td>Time from ICU admission</td>
<td>161 hours</td>
<td>51 hours</td>
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Palevsky et al *NEJM* 2008
Bellomo et al *NEJM* 2009
Side note: What does “timing” really mean?

• *Is it really feasible to design a strategy for managing AKI based on actual time from AKI onset?*

• perhaps only in setting of known insult when there is close serial monitoring (eg, cardiac surgery, elective angiography)

• in the majority of situations, the true duration of AKI is unknown
What does “timing” really mean?

• the notion of “early” RRT initiation may be a bit of a misnomer

• more practically, an “early” start signifies the initiation of RRT when no urgent indication for RRT exists

• concept of “pre-emptive” RRT initiation
Conventional indications and RRT initiation

• FINNAKI Study
• 2901 critically ill patients accrued from 17 ICUs in Finland from Sept/11-Feb/12
• 239 patients who commenced RRT
• Classic RRT = presence of at least one indication before RRT initiation
• Pre-emptive RRT = no conventional indication present at time of RRT initiation

Vaara et al CJASN 2014
Conventional indications and RRT initiation

CLASSIC RRT (n=134)
- presence of ≥ 1:
  - $[K^+] > 6$ mmol/L
  - pH < 7.15
  - urea > 100.8 mg/dL
  - oliguria/anuria
  - fluid overload

Delayed (n=44)  Urgent (n=90)

90 day Mortality:
- 68%
- 35%

PRE-EMPTIVE RRT (n=105)

30%

Vaara et al CJASN 2014
Conventional indications and RRT initiation: Mortality

- Classic vs pre-emptive initiation
  - Adjusted OR 2.05 (95% CI 1.03-4.09)
- Classic-delayed vs classic-urgent
  - Adjusted OR 3.85 (95% CI 1.48-10.22)

Vaara et al. *CJASN* 2014
Take home message from these studies

- Earlier RRT initiation, defined in different ways, looks like a promising strategy
- *Not so fast*....
- all patients in these studies got RRT
- in clinical practice, some individuals with severe AKI recover kidney function
- if such patients were included in the “late” groups in the previous studies, the association between late RRT and death would likely be attenuated
Fundamental problem with existing timing data

• Inability to compare any initiation strategy with “real life” in which some patients die or recover kidney function spontaneously

“I believe that prompt and prophylactic initiation of RRT is beneficial in certain patients. Unfortunately, I am not sure who those patients are.”

- F. Perry Wilson, MD CJASN 2014
Reasons to be cautious about a strategy of earlier RRT

• unmeasured confounding in observational studies
• can’t be certain that individuals with high BUNs were not inherently different from those with low BUNs at the time of RRT initiation
• the only solution is to conduct an RCT…
Completed trials examining RRT initiation in AKI

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 30: 2205–2211, 2002
Inclusion Criteria

- u/o < 30 mL/h x 6 hours
- CrCl < 30 mL/min
- mechanically ventilated
- plan for > 3 days in ICU

EARLY HEMOFILTRATION
- start within 12 hrs of inclusion criteria being met

LATE HEMOFILTRATION
- start when urea > 40 mmol/L or K > 6.5 mmol/L or CHF
### Approximate timing parameters

<table>
<thead>
<tr>
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<th>Early start (n=70)</th>
<th>Late start (n=30)</th>
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<tbody>
<tr>
<td>Time from inclusion to RRT (hrs)</td>
<td>7 hrs</td>
<td>42 hrs</td>
</tr>
<tr>
<td>Urea at time of RRT initiation (mg/dL)</td>
<td>48</td>
<td>103</td>
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Bouman et. al. *Crit Care Med* 2002
Trial results

• 28-day mortality
  EARLY: 29%
  LATE: 25%

• all surviving patients recovered renal function

Bouman et. al. *Crit Care Med* 2002
Limitations

- underpowered for more subtle- and realistic- survival differences
- preponderance of cardiac surgery patients
- overall, an inconclusive trial

Bouman et. al. *Crit Care Med* 2002
A more recent trial

- open label RCT of 202 patients with severe AKI (thresholds unclear)
- single centre in Western India
- **Earlier-start RRT:** Commence RRT when sCr > 7 mg/dL and/or BUN > 70 mg/dL
- **Usual-start RRT:** Clinician judgment guides RRT initiation

Jamale et al *AJKD* 2013
Study population

• Mean age 42 y
• > 50% of AKI related to tropical infections and obstetric complications
• 17% of patients in the usual-start group recovered before initiation of RRT
• Mean sCr at RRT initiation:
  7.43 mg/dL (earlier-start)
  vs 10.49 mg/dL (usual start)

Jamale et al AJKD 2013
Results

• 90-day mortality
  Earlier-start: 21%
  Usual-start: 12%
  RR 1.67 (95% CI, 0.88-3.17)

Jamale et al AJKD 2013
Limitations

• patient characteristics differ from AKI population in North America
• Not an ICU population
• Small sample size, wide confidence intervals
• Were criteria for RRT initiation in the earlier-start arm actually too late?

Jamale et al AJKD 2013
Why is a definitive trial needed?

• reasonable rationale for why earlier/pre-emptive RRT may be beneficial
• pre-emptive RRT is already standard of care at many centres
• a pre-emptive or early RRT strategy may harm patients who will otherwise recover and is resource intense
• the trials conducted to date have been inconclusive
Ongoing RCTs: IDEAL-ICU

- Clinicaltrials.gov identifier NCT01682590
- Multicentre RCT in France
- Planned enrollment of 864 patients with septic shock and RIFLE-F AKI
- **Early initiation:** within 12 hours of meeting AKI criteria
- **Delayed initiation:** 48-60 hours following enrollment or emergency indication
- **Primary outcome:** 90-day mortality

Barbar et al. *Trials* 2014
Artificial Kidney Initiation in Acute Kidney Injury (AKIKI) Trial

- ClinicalTrials.gov Identifier NCT01932190
- planned enrollment of 620 patients with KDIGO Stage 3 AKI receiving mechanical ventilation and pressors

- Early initiation: commence RRT when KDIGO 3 AKI noted
- Delayed initiation: commence RRT only in presence of an “alert criterion”

- Primary outcome: 60-day mortality

Gaudry et al J Crit Care 2014
The STandard vs Accelerated initiation of Renal Replacement Therapy in AKI Trial

STARRT-AKI

- Randomized, open-label trial of accelerated vs standard initiation of RRT in critically ill patients with AKI
- 2,866 patients with KDIGO Stage 2-3
- 80 centres in Canada, USA, Australia, New Zealand, UK, Ireland, Austria and Finland
- ClinicalTrials.gov Identifier: NCT02568722
Concealed Random Block Allocation Stratified by Centre

**Accelerated RRT initiation**
Start RRT no more than 12 hr after becoming eligible

**Standard RRT initiation**
*RRT permitted upon ≥ 1 of following:*

- \([K^+] \geq 6.0 \text{ mmol/L}\)
- pH \(\leq 7.20\) or \(\text{HCO}_3^- \leq 12 \text{ mmol/L}\)
- \(\text{PaO}_2/\text{FiO}_2 \leq 200\) and perception of clinically significant FO
- Persistent AKI for > 72 hr

**Primary Outcome:** All-cause mortality at 90 days

**Secondary Outcomes:** RRT dependence, residual kidney damage, health-related quality of life at 90 days; health care costs through one year
Pilot trial completed

- 100 patients
- 12 sites in Canada
- Feasibility of recruitment, protocol implementation and 90-day follow-up demonstrated
- No safety signal

Median 24 hour difference to RRT initiation between groups
25% of patients in the standard arm survived without commencing RRT

Wald et al Kidney Int 2015
Timing of RRT in AKI: Final points

- current clinical practice is highly variable
- initiation of RRT before life-threatening indications are evident has become increasingly accepted
- this approach has plausible benefits but also significant potential for harm
- definitive RCTs will hopefully enhance the quality of evidence and guide decision-making
Thank you for your attention

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