Indications and timing of renal replacement therapy

Rolando Claure-Del Granado¹ and Etienne Macedo²

¹Hospital Obrero #2 – CNS, Universidad Mayor de San Simon, School of Medicine, Cochabamba, Bolivia; ²Department of Medicine, Nephrology Division, University of California San Diego, EE.UU.

Abstract

The management of patients with acute kidney injury is mainly supportive in nature, with no available proven therapeutic modalities to treat the condition. Renal replacement therapy (RRT) is indicated in patients with severe kidney injury, or increased volume or metabolic demands. In the absence of clinically significant uremic symptoms or specific indications such as severe electrolyte abnormalities or volume overload, the optimal timing of RRT initiation is controversial. Randomized, controlled trials that have compared strategies of early versus delayed initiation of RRT in the absence of obvious indications have yielded conflicting results. The implementation of decision support systems is challenging but could provide clinicians a framework with specific recommendations for interventions. Recently, some algorithms have been proposed to guide physicians in the decision to initiate, and their application in clinical practice may reduce variations across physicians and centers. The decision on the appropriate time to start RRT is complex, integrating numerous variables, and should largely be individualized, however the lack of definitive parameters to define early or late initiation reveals a great need to continue research on this field. Such evidence is important for reducing variations in the clinical practice of RRT prescription and improving patient outcomes.


Resumen

El tratamiento de la lesión renal aguda es principalmente de soporte, ya que no se disponen de terapias efectivas para tratar esta enfermedad. La terapia de reemplazo renal (TRR) esta indicada en pacientes con lesión renal aguda secundaria a sep- sis grave, o cuando existen demandas metabólicas incrementadas o sobrecarga de volumen. El tiempo de inicio óptimo de TRR en ausencia de síndrome urémico clínicamente significativo, o cuando existen indicaciones específicas como alteraciones en los electrolitos o sobrecarga de volumen es controversial. Estudios clínicos aleatorizados y controlados que han compara- do estrategias de inicio temprano versus inicio tardío de TRR han mostrado resultados contradictorios. La implementación de un sistema de soporte para la toma de decisiones constituye un reto, pero podría proveer a los clínicos una estructura con recomendaciones específicas para intervenciones terapéuticas. Recientemente, se han propuesto algunos algoritmos para guiar a los médicos en la toma de decisiones acerca de cuando iniciar la TRR, y la aplicación de estos algoritmos en la práctica clínica podría reducir la variabilidad en relación a la toma de decisiones entre diferentes médicos y centros. La decisión en cuanto al tiempo ideal de inicio de TRR es complejo, integra varias variables, y debiera ser individualizado; sin embargo, la falta de parámetros categóricos para definir un inicio temprano versus un inicio tardío nos muestran la necesidad de seguir investigando en esta área. Tal evidencia es importante para reducir la variaciones en la práctica clínica de la prescripción de TRR y para mejorar los desenlaces en los pacientes.


Correspondence:
Rolando Claure-Del Granado
Hospital Obrego #2 – C.N.S.
Universidad Mayor de San Simon, School of Medicine
Cochabamba, Bolivia
E-mail: rclaure@yahoo.com

Date of reception: 23-11-2017
Date of acceptance: 08-03-2018
DOI: 10.24875/GMM.M18000068

Contents available at PubMed
www.anmm.org.mx
Introduction

When renal function acutely declines, and fluid and metabolic demands are increased, renal replacement therapy (RRT) is the only available treatment for acute kidney injury (AKI). However, in the absence of life-threatening situations, the tendency is to avoid RRT as long as possible. This thought process reflects the decisions made for patients with end-stage renal disease in whom the initiation of RRT is associated with dialysis dependency. In critically ill patients with AKI, absolute indications for RRT include: severe acidosis, fluid overload with oliguria that does not respond to the use of diuretics, hyperkalemia, and signs/symptoms of uremia. In the absence of absolute or urgent life-threatening indications, the optimal time to start RRT is unknown. Nevertheless, the presence of AKI complications such as signs/symptoms of uremia can increase AKI mortality risk and be considered “late” for dialysis initiation (Table 1). A better approach to evaluate timing for RRT initiation would be based on clinical criteria including presence and degree of other organs dysfunction, rather than biochemical evidence of uremia. Early intervention would allow for better control of fluids and solutes and promote the return of renal function. The benefits of supporting other organs depend on the balance between the current load associated with the clinical conditions and the ability of the kidneys to manage fluid and the metabolic load. Consequently, the initiation of RRT should be prompted by the inability of the kidney to meet the demands being placed on them. Although a recent study shows that clinicians are less commonly utilizing AKI staging as a criterion for initiating RRT, the tendency is still to delay initiation if renal recovery is possible. Concerns associated with the RRT procedure such as hypotension, arrhythmias, and complications with the vascular access and the use of anticoagulation is the most common reasons to avoid RRT. In addition, the potentially deleterious effect of “early” RRT initiation on renal recovery caused by hemodynamic instability, and vascular catheter-related bacteremia and sepsis further delay the decision to initiate it.

Defining timing of RRT Initiation

There is no consensus on how to properly define timing of RRT initiation in AKI. Most studies that have addressed the issue of timing have used several terms for their study methodologies such as “early,” “accelerated,” “delayed,” “late,” and “standard” initiation of RRT and have applied various definitions to differentiate early versus late initiation of RRT. It is important to mention that early or late initiation of RRT will depend on the clinical context of each individual patient, making the use of these terms relative. The definitions used for timing in RRT have integrated physiological parameters such as urine output and biochemical parameters such as serum creatinine, timing relative to the development of AKI, timing relative to hospital or ICU admission, and timing relative to complications of AKI, or conventional indications for starting RRT such as hyperkalemia, acidosis, or fluid overload. This heterogeneity in how the timing and the threshold for starting RRT have been defined represent significant challenges and fundamental obstacles in progress on this field. Furthermore, one aspect that most studies have not considered is withholding RRT. It is possible that conservative management of these patients consisting of supportive management, watchful waiting, and initiation of RRT only when absolute or urgent indications develop may, in fact, result in the spontaneous recovery of kidney function by patients with severe AKI. Recently a multicenter randomized controlled trial showed that 25% of patients randomized to a strategy of standard initiation of RRT recovered kidney function without receiving RRT. In the standard arm at 90 days following enrollment, the mortality rate was 37% versus 38% in the accelerated arm.

Current clinical practice guidelines

At present, we have two clinical practice guidelines for AKI that have made recommendations regarding the issue of timing of RRT: the kidney disease improving global outcomes (KDIGO) Consortium and the National Institute for Health and Care Excellence (NICE) in the United Kingdom.

The KDIGO guidelines provided the following consensus recommendations:

a. Initiate RRT emergently when life-threatening changes in a fluid, electrolyte, and acid-base balance exist (not rated).

b. Consider the broader clinical context, the presence of conditions that can be modified by RRT, and trends of laboratory test results rather than absolute values of blood urea nitrogen (BUN) or serum creatinine when making the decision of when to start RRT (not rated).
The KDIGO guidelines leave the final decision to start RRT to the attending physician in the context of deterioration of kidney function or any worsening of the patient clinical condition, without any definitive recommendation.

Similarly, the NICE clinical practice guidelines for AKI have proposed the following recommendations:

a. Immediately discuss any potential indication of RRT with a nephrologists and/or a critical care specialist to ensure that the therapy is started as soon as needed.

b. Immediately refer patients for RRT if any of the following are not responding to medical management:
   - Hyperkalemia
   - Metabolic Acidosis
   - Complications of uremia (e.g., pericarditis and encephalopathy)
   - Fluid overload
   - Pulmonary edema.

c. Base the decision of when to start RRT on the condition of the patient as a whole rather than on isolated indicator such as the BUN, creatinine, or potassium level.

Like KDIGO Clinical Practice Guidelines, NICE Guidelines also recognized the paucity of high-quality evidence for decision-making about when to start RRT. NICE guidelines also highlight the need of better tools such as biomarkers or risk prediction scores that would allow clinicians to better discriminate patients who have a high probability of developing worsened AKI or complications related to AKI in whom RRT will benefit from patients who have a high probability of recovering kidney function and who may benefit from conservative strategy.

What evidence we currently have?

Several studies have recently tried to address the question of timing in RRT in critically ill patients with AKI. A summary of these trials is shown in table 2. Observational studies have suggested that early RRT may improve survival\textsuperscript{10,11,16}; however, conclusions that could be drawn from available observational data are limited because of the retrospective design of the study or post hoc analysis, the heterogeneity of the cohort, and the different definitions and thresholds for RRT initiation. Another issue with observational studies is that they did not compare patients with AKI that received RRT with patients who did not; except for the Finish AKI (FINNAKI) study\textsuperscript{17}. This study included 239 critically ill patients with AKI and treated with RRT. The FINNAKI study compared 3 timing RRT strategies: pre-emptive if RRT was started in the absence of hyperkalemia, severe academia, uremia, oligoanuria, and fluid overload with pulmonary edema; “classic-urgent” if started within 12 h of developing one of the indications mentioned above; and “classic-delayed” if started > 12 h after developing one of these indications. “Pre-emptive” RRT was associated with lower 90-day mortality as compared to “classic-urgent” RRT (30 vs. 49%; odds ratio 2.1, 95% CI, 1.0-4.1). This same association was found when “classic-urgent” RRT was compared to “classic-delayed” RRT (39 vs.

<table>
<thead>
<tr>
<th>Indications</th>
<th>Absolute</th>
<th>Relative</th>
<th>Relative contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic disorders</td>
<td>– BUN &gt; 100 mg/dl</td>
<td>– BUN &gt; 76 mg/dl</td>
<td>– Futility prognosis</td>
</tr>
<tr>
<td></td>
<td>– Hyperkalemia &gt; 6 mEq/l</td>
<td>– Hyperkalemia &gt; 6 mEq/l</td>
<td>– Patient receiving palliative care</td>
</tr>
<tr>
<td></td>
<td>with ECG abnormalities</td>
<td>– Hyperkalemia &gt; 6 mEq/l</td>
<td>– High likelihood of non-recovery of renal function in a patient who is not a candidate for long-term dialysis</td>
</tr>
<tr>
<td></td>
<td>– Hypermagnesemia &gt; 8 mEq/l</td>
<td>– Hypokalemia &gt; 6 mEq/l</td>
<td></td>
</tr>
<tr>
<td></td>
<td>with anuria and absent deep tendon reflexes</td>
<td>– Hypokalemia &gt; 6 mEq/l</td>
<td></td>
</tr>
<tr>
<td>Acidosis</td>
<td>– pH &lt; 7.15</td>
<td>pH &gt; 7.15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Lactic acidosis related to metformin use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oliguria/Anuria</td>
<td>AKIN stage 1, 2 or 3</td>
<td>Diuretic resistant</td>
<td></td>
</tr>
<tr>
<td>Fluid overload</td>
<td>Diuretic sensitive</td>
<td>Concomitant accumulation of poisons or toxic drugs that can be removed by RRT (e.g., salicylates, ethylene glycol, methanol, metformin)</td>
<td></td>
</tr>
<tr>
<td>Overdose/toxicity</td>
<td>From a dialyzable drug or toxin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BUN: blood urea nitrogen; ECG: electrocardiogram; AKIN: acute kidney injury network; RRT: renal replacement therapy.
Table 2. Summary of randomized controlled trials addressing the question of timing in renal replacement therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Type of RCT</th>
<th>Type of RRT</th>
<th>Patient population</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conger et al.</td>
<td>n=18</td>
<td>Single center</td>
<td>IHD</td>
<td>Adult major trauma</td>
<td>Urea &gt;106.9 mg/dL or sCr &gt;4.9 mg/dL</td>
<td>Mortality: 38% vs. 80%</td>
</tr>
<tr>
<td>Pursanini et al.</td>
<td>n=35</td>
<td>Single center</td>
<td>IHD</td>
<td>Adult medical/obstetrical</td>
<td>Urea &gt;257.1 mg/dL or sCr &gt;7 mg/dL</td>
<td>Mortality: 22% vs. 29%</td>
</tr>
<tr>
<td>Sugahara et al.</td>
<td>n=28</td>
<td>Single center</td>
<td>PIRRT</td>
<td>Adult cardiac surgery</td>
<td>UO &lt;30 ml/h x 3 h and sCr &lt;11.7 mg/dL</td>
<td>Mortality: 14% vs. 86%</td>
</tr>
<tr>
<td>Durmaz et al.</td>
<td>n=44</td>
<td>Single center</td>
<td>IHD</td>
<td>Adult CKD, cardiac surgery</td>
<td>10% rise of sCr from pre-operative value</td>
<td>Mortality: 5% vs. 30%</td>
</tr>
<tr>
<td>Bouman et al.</td>
<td>n=106</td>
<td>2 centers</td>
<td>CVVH</td>
<td>Adult critically ill+shock</td>
<td>UO &lt;30 ml/h x 6 h and CrCl &lt;20 ml/min</td>
<td>Mortality: 29% vs. 25% Recovery no difference</td>
</tr>
<tr>
<td>Jamale et al.</td>
<td>n=208</td>
<td>Single center</td>
<td>IHD</td>
<td>Adult community acquired AKI</td>
<td>Urea &gt;150 mg/dl and/or sCr &gt;7.0 mg/dL</td>
<td>Mortality: 21% vs. 12%; renal recovery (dialysis dependence at 3 months) 5% vs. 5%</td>
</tr>
<tr>
<td>Wald et al.</td>
<td>n=100</td>
<td>Multicenter</td>
<td>Mixed</td>
<td>Adult critically ill</td>
<td>Two fold increase of sCr; UO &lt;6 ml/kg x 12 h; and blood NGAL &gt;400 ng/ml</td>
<td>Mortality: 38% vs. 37%; renal recovery (dialysis dependence at 90 days) 0% vs. 6%</td>
</tr>
<tr>
<td>Gaudry et al.</td>
<td>n=620</td>
<td>Multicenter</td>
<td>Mixed</td>
<td>Adult critically ill</td>
<td>RRT within 6 hours after documentation of severe AKI (KDIGO stage 3)</td>
<td>Mortality: 48.5% vs. 49.7%</td>
</tr>
<tr>
<td>Zarbock et al.</td>
<td>n=231</td>
<td>Single center</td>
<td>CVVHDF</td>
<td>Adult critically ill</td>
<td>RRT within 8 hours after AKI diagnosis (KDIGO stage 2)</td>
<td>Mortality: 39.3% vs. 54.7%; renal recovery 53.6% vs. 38.7</td>
</tr>
</tbody>
</table>

RRT: Renal replacement therapy; IHD: intermittent hemodialysis; PIRRT: prolonged intermittent renal replacement therapy; CRRT: continuous renal replacement therapy; CVVH: continuous veno-venous hemodiafiltration; CVVHDF: continuous veno-venous hemodiafiltration; AKI: acute kidney injury; CKD: chronic kidney disease; sCr: serum creatinine; UO: urine output; CrCl: creatinine clearance; RCT: randomized controlled trial; KDIGO: Kidney disease improving global outcomes.
Several small prospective randomized trials have been recently performed. Most of these are the observational studies, we mentioned above which show some beneficial effects of an early initiation of RRT in critically ill patients with AKI\textsuperscript{18-20}.

However, a meta-analysis of 10 randomized trials showed no benefit of early initiation on 30-day, 60-day, or 90-day mortality\textsuperscript{21}. There was also no difference showed no benefit of early initiation on 30-day, 60-day, or 90-day mortality\textsuperscript{21}. There was also no difference between early and late initiation on the risk of dialysis dependence, length of intensive care unit or hospital stay, or recovery of renal function. However, this analysis is also limited in part because of the heterogeneity due to variable definitions of early versus late initiation.

Three of the largest trials that were included in this meta-analysis demonstrated no benefit with earlier initiation of RRT\textsuperscript{14,22,23}. The best data are from the artificial kidney initiation in kidney injury trial, a multicenter, randomized trial that included 620 patients that had severe AKI and required either mechanical ventilation, catecholamine infusion, or both\textsuperscript{22}. Severe AKI was defined using KDIGO Stage 3 criteria (an increase in serum creatinine to 3 times baseline, or increase in serum creatinine to $\geq 4.0$ mg/dL, or reduction in urine output to $< 0.3$ mL/kg/h for $\geq 24$ h, or anuria for $\geq 12$ h). Patients were excluded if they had BUN $> 112$ mg/dL, serum potassium $> 6$ Eq/L (or $> 5.5$ mEq/L despite medical intervention), $pH < 7.15$, or pulmonary edema (requirement for oxygen flow rate $> 5$ L/min to maintain $O_2$ saturation $> 95\%$ or among intubated patients and requirement for fraction of inspired oxygen $> 50\%$). These patients were excluded because they were considered to have an “urgent” indication for RRT.

Patients were assigned to a strategy of early RRT (within 6 h after documentation of severe AKI) or to a strategy of delayed RRT initiation (initiation after the onset of severe hyperkalemia, metabolic acidosis, or pulmonary edema, all defined by parameters included in the exclusion criteria listed above, or after an increase in BUN $> 112$ mg/dL, or development of oliguria for more than 72 h after randomization).

The study showed no benefit associated with the early RRT strategy. Mortality at 60 days was not different between the early and late strategy groups (48.5% vs. 49.7%, respectively; $p = 0.79$). 49% of the patients in the delayed strategy group never received RRT. Diuresis occurred earlier in the delayed-strategy group, possibly suggesting a renal recovery in this group. Compared with the delayed strategy group, catheter-related infections (5% vs. 10%), and hypophosphatemia (5% vs. 22%) were more common in the early strategy group.

The other two studies were smaller and have also shown no benefit associated with early initiation, although results need to be interpreted with caution as both trials were underpowered to detect mortality differences\textsuperscript{14,23}.

The early versus late initiation of RRT in critically ill patients with AKI (ELAIN) study was a single-center, randomized trial that showed a survival benefit conferred by early initiation of RRT\textsuperscript{24}. This trial included 231 critically ill patients with moderate AKI, as defined by KDIGO Stage 2 criteria (including creatinine $\geq 2$ times baseline or urinary output $< 0.5$ mL/kg/h). All patients also had severe sepsis, required vasopressors, or had refractory volume overload. Patients were assigned to early RRT initiation (within 8 h of AKI diagnosis) or delayed or no initiation. Patients in the delayed or no initiation group received RRT within 12 h after the patient achieved KDIGO Stage 3 criteria or developed an indication for RRT (such as serum urea level $> 100$ mg/dL, potassium $> 6$ mEq/L, serum magnesium $> 8$ mEq/L, urine output $200$ mL over 12 h, or diuretic-resistant edema). In the delayed initiation group, 11 patients ended up not receiving RRT; of these, only six patients did not progress to Stage 3, three patients had a recovery of renal function, and three patients died. Compared with delayed or no initiation, early RRT initiation reduced 90-day mortality (hazard ratio, 0.66, 95% CI 0.45-0.97). Furthermore, more patients recovered renal function in the early versus delayed group by 90 days (odds ratio 0.55, 95% CI 0.32-0.93), and both the duration of RRT and the hospital stay were shorter in the early-initiation group. However, although this was a carefully performed trial, it is difficult to understand how such small differences in the timing of dialysis initiation could achieve such improvement in outcomes.

Other randomized trials, including Initiation of Dialysis Early versus Delayed in Intensive Care Unit (IDEAL-ICU; NCT01682590) and Standard versus Accelerated Initiation of RRT in AKI (STARRT-AKI; NCT02568722), are underway and may allow more definitive conclusions to be drawn.

**Some proposed approaches**

In light of contradictory results of the observational studies and a clinical trial evaluating the effect of
timing of RRT, some approaches have been proposed. Bagshaw et al.\textsuperscript{25} algorithm incorporate several patient-specific factors, based on evidence when available, that may decisively influence when to initiate RRT. In this algorithm, RRT is initiated if there is an absolute indication. If there is no absolute indication, it recommends optimizing resuscitation and the continuous assessment of: AKI severity and trend, illness severity and trajectory, and finally the response to resuscitation optimization (e.g. intravascular volume, cardiac output, and mean arterial blood pressure). If patient progressed to AKI Stage 3, the authors recommend considering RRT. If patient is on AKI Stage 1 or 2, it is also suggested to consider initiation of RRT if any of the following situations are identified: rapidly worsening AKI or illness severity, hypercatabolic state, refractory fluid overload and/or accumulation, severe sepsis, permissive hypercapnia, reduce renal reserve, and low probability for early renal recovery.

More recently Mendu et al.\textsuperscript{26} proposed a decision-making algorithm for RRT initiation and discontinuation. The AKI Standardized Clinical Assessment and Management Plan algorithm provides recommendations to assist clinicians in deciding when to initiate or withhold dialysis on the basis of patient comorbidities and clinical parameters. They divided indications to start RRT into MORE URGENT and LESS URGENT, and they use the acronym AEIOU (A = acidosis; E = Electrolyte; I = Ingestion; O = Overload; and U = Uremia) to evaluate important clinical aspects that will determine the decision to start RRT. If any of the MORE URGENT indications to start RRT is present, they recommend initiating RRT; or if ≥ 3 LESS URGENT indications are present. In the case of 1-2 less urgent indications, authors suggest withholding RRT. The authors also recommend not starting RRT in the patient has all the following non-urgent characteristics: pH > 7.3 or not available, K < 6.0 mmoL/L, no ingestion of toxins, ≤ 1+ edema, urine output > 500 mL day, and BUN < 60 mg/ dL (Fig. 1).

**Conclusions**

Based on recent observational and clinical trials, the optimal time for RRT initiation in critically ill patients...
with AKI is uncertain. Recent high-quality randomized controlled trials specifically focused on when to start RRT have shown conflicting results. Implementing a decision support system is challenging but could provide clinicians a framework with specific recommendations for interventions. Proposed algorithms could reduce practice variations across physicians and centers. Clearly, there is a great need to continue research in this field. Such evidence is important for reducing unnecessary variations in the clinical practice of RRT prescription. At present, the decision on when to start RRT is complex and should largely be individualized for each patient.

References
