Renal Replacement Therapy in Acute Kidney Injury

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Abstract

Acute kidney injury (AKI) is a common and serious complication in critically ill patients. The mortality rate remains high despite improved renal replacement techniques. A possible cause of the high mortality rate is that intensive care unit patients tend to be older and more debilitated. Pathophysiological factors associated with AKI are also incriminated in the failure of other organs, indicating that AKI is often part of a multiple organ failure syndrome. The management of patients with AKI is principally supportive. Renal replacement therapy (RRT) was indicated for patients with severe kidney injury and multiple modalities of RRT are currently available. These include intermittent hemodialysis, continuous renal replacement therapies, and hybrid therapies, such as sustained low-efficiency dialysis. This article reviews current knowledge regarding the optimal timing, appropriate type of modality and dosing strategy for patients with AKI who require RRT.

KEY WORDS: continuous renal replacement therapies, intermittent hemodialysis, sustained low-efficiency dialysis, intensive care unit

Introduction to Acute Kidney Injury

Acute kidney injury (AKI) is well recognized for its impact on intensive care unit (ICU) patient outcome (1-4). In patients with severe AKI requiring renal replacement therapy (RRT), mortality is approximately 50% to 70% (4). In an international survey, more than 200 different definitions of AKI were reported (5). The numerous definitions cause clinical confusion and complicate data comparison (6, 7). The risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage renal failure (RIFLE) criteria were published by the Acute Dialysis Quality Initiative (ADQI) group in 2004, in an attempt to standardize AKI research (1). It classified AKI into three categories (risk, injury, and failure) according to the status of the patient’s serum creatinine (SCr) level and urine output (UO).

In 2007, the Acute Kidney Injury Network (AKIN) group proposed a modified version of the RIFLE criteria. In AKIN stage-1 (analogous to RIFLE-Risk), a smaller change within 48 hours in SCr exceeding 0.3 mg/dL (≥ 26.2 µmol/L) was suggested as an AKI threshold. Additionally, patients receiving RRT were re-classified as AKIN stage-3 (RIFLE-Failure). Finally, the Loss and End-stage kidney disease categories were eliminated in AKIN classification (8). The use of consensus definitions of AKI (RIFLE and AKIN) in the literature has increased substantially to date (9-22). Both classifications have proved to be useful for diagnosing and classifying AKI severity in critically ill patients.

Indications for Initiation of Dialysis

RRT is indicated for acute management of life-threatening complications of AKI (23). These include:

(A) Acidosis: metabolic acidosis (pH < 7.1);
(E) Electrolyte imbalance: hyperkalemia (plasma potassium concentration > 6.5 meq/L) or rapidly rising potassium levels;
(I) Intoxications: certain alcohol and drug...
intoxications;

(O) **Overflow:** fluid overload refractory to diuretics;

(U) **Uremic symptoms and/or signs:** signs of uremia such as pericarditis, neuropathy, or an otherwise unexplained decline in mental status.

Whether it is beneficial to initiate RRT for volume management at an early stage or to escalate the dose of diuretic is not known.

Determination of the optimal timing for initiation of RRT in patients with AKI will require an adequately powered prospective randomized trial. Adequate design of such a trial is limited by the current inability to prospectively and quickly identify patients with early AKI who will have protracted renal injury and eventually require RRT. Therefore, it is not possible to provide evidence-based criteria for the initiation of RRT in AKI (24).

The recently published Kidney Disease Improving Global Outcomes (KDIGO) guidelines provide a welcome and timely synthesis of the evidence base to support the management of AKI. KDIGO utilized a grading system with level 1 being rated a ‘strong recommendation’, implying that most patients ‘should’ receive a particular action. In contrast, level 2 guidelines are essentially ‘suggestions’ and are deemed ‘weak’ or discretionary, recognizing that management decisions may vary in different clinical contexts. Each recommendation was further graded from A to D by the quality of evidence underpinning them, with grade A referring to a high quality of evidence whilst grade D recognizing a ‘very low’ evidence base. According to the guidelines, the optimal timing of dialysis for AKI is as follows (25):

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

2: **Consider the broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests—rather than single blood urea nitrogen (BUN) and creatinine thresholds alone—when making the decision to start RRT.** (Not Graded)

**Optimal Modality**

A large number of modalities are available for RRT. These include intermittent hemodialysis (IHD), peritoneal dialysis (PD), continuous renal replacement therapy (CRRT), and hybrid therapies such as sustained low-efficiency dialysis (SLED). Experience with PD in AKI is limited, except in the pediatric setting and in regions with limited resources (23).

**CRRT**

The choice of dialytic technique is dependent on various factors that include availability of each technique, expertise of the clinician, patient’s hemodynamic stability and comorbid conditions, and degree to which solutes and/or fluid must be removed. In general, CRRTs are most often selected for patients with AKI whose hemodynamic instability precludes the use of IHD. CRRT represents a family of modalities that provide continuous support for severely ill patients with AKI. These include continuous hemofiltration (HF), hemodialysis (HD), and hemodiafiltration (HDF) and involve both convective and diffusive therapies. Although convective therapies (i.e., HF) are associated with better clearance of medium- and large-molecular-weight molecules as compared with diffusive therapies (i.e., HD), there are no studies that clearly show improved clinical outcomes with a particular type of solute transport (24).

**CRRT vs. IHD**

The theoretical advantages of CRRT over IHD are slower fluid removal, which results in greater hemodynamic stability and better control of fluid balance; slower control of solute concentration, which avoids large fluctuations and fluid shifts (including a reduced risk of development of—or an increase in—cerebral edema); great flexibility, which allows adaptation of the treatment to the patient’s needs at any time; and the fact that treatment can be performed with relatively simple and user-friendly machines, which allows critical-care nurses to monitor the treatment. Disadvantages include need for immobilization of the patient, use of continuous anticoagulation, risk of hypothermia and, in some settings, higher costs. The major advantages of IHD over CRRT are faster removal of toxins and restricted treatment period, which allows time for other diagnostic and therapeutic interventions. IHD may, therefore, be the preferred treatment in cases where immediate removal of small solutes is required, such as in patients with severe hyperkalemia, poisoning, and tumor lysis syndrome. Hybrid treatments, such as SLED, may share some of the advantages of both IHD and CRRT while no having the disadvantages of the two techniques (Table 1) (23, 24).

The two principal outcomes of CRRT and IHD that have been examined are patient survival and recovery of renal function. Although there is a paucity of evidence on these issues, current data suggest that patient survival and recovery of renal function are similar for both CRRT and IHD. The data do not support the superiority of any particular mode of RRT in patients with AKI; thus, for most patients, the selection...
of modality should be made according to local expertise and availability of staff and equipment. Other factors may prevail in selected patients. For example, for patients with acute brain injury or fulminant hepatic failure, continuous therapy may be associated with better preservation of cerebral perfusion.

**SLED**

Many centers have begun utilizing dialysis machines to deliver a dialysate flow at only 100 mL/min for periods ranging from 8 h to 24 h per day. Advantages of this technique include a high hemodynamic tolerance and an unsurpassed solute removal capability. This dialytic intervention is named SLED or extended daily dialysis (EDD). “Hybrid hemodialysis” is probably a better and more inclusive descriptive term for these therapies.

The SLED/EDD hybrid technique offers every advantage of CRRT, but it does not require any new equipment acquisition because some hemodialysis machines can also be used for regular hemodialysis treatments. Therefore, SLED/EDD hybrids are well suited for centers in which there is limited support for CRRT. The therapy can be applied to all patients with AKI requiring dialytic supports that manifest intolerance to regular hemodialysis. Probably the most common usage of these hybrid techniques has been as a bridge between CRRT and IHD.

**CRRT vs. SLED**

CRRT lacks the advantage in terms of patient survival and it is also more expensive than IHD and associated with a number of obstacles such as patient immobilization required for anticoagulation, as well as need of specialized machines and premixed commercial solutions. These drawbacks have stimulated a search for strategies that can incorporate the putative hemodynamic benefits of CRRT without the associated logistic and resource constraints. SLED meets many of these criteria.

Observational data from single centers suggest that SLED is a feasible way of providing RRT that is adequate, hemodynamically well tolerated, potentially anticoagulation-free, and possibly cost-effective. However, three small studies have compared SLED and CRRT. Using invasive cardiac monitoring, they did not find any significant differences in any measured hemodynamic parameter (mean arterial pressure, systemic vascular resistance, and cardiac output) between the two groups of patients, and the two methods achieved comparable removal of creatinine and urea. Another study randomized 16 patients to receive three sessions with either CVVH or SLED (with an added HF component) and showed that fluid removal and hemodynamic parameters were similar in both groups.

Table 1. Parameters for comparison of renal replacement therapy in acute kidney injury

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IHD</th>
<th>SLED</th>
<th>CRRT</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodynamic stability</td>
<td>Unstable</td>
<td>Between IHD and CRRT</td>
<td>Stable</td>
<td>Stable</td>
</tr>
<tr>
<td>Fluid removal</td>
<td>Rapid, harsh, incomplete</td>
<td>Between IHD and CRRT</td>
<td>Slow, gentle, complete</td>
<td>Slow, gentle, incomplete</td>
</tr>
<tr>
<td>Dialysis efficiency</td>
<td>High efficiency, short time</td>
<td>Between IHD and CRRT</td>
<td>Low efficiency, long time</td>
<td>Low efficiency, long time</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>Zero heparin possible</td>
<td>Zero heparin possible</td>
<td>Frequently necessary</td>
<td>Zero heparin</td>
</tr>
<tr>
<td>Patient mobilization</td>
<td>Possible</td>
<td>Possible*</td>
<td>Possible*</td>
<td>Possible</td>
</tr>
<tr>
<td>Specialty personnel</td>
<td>Definitely</td>
<td>Definitely</td>
<td>Perhaps</td>
<td>Unessential</td>
</tr>
<tr>
<td>Drug dosing/delivery</td>
<td>Difficult</td>
<td>Difficult</td>
<td>Easier</td>
<td>Easier</td>
</tr>
<tr>
<td>Volume restriction</td>
<td>Significant</td>
<td>Between IHD and CRRT</td>
<td>Minimal</td>
<td>Significant</td>
</tr>
</tbody>
</table>

Abbreviations: IHD, intermittent hemodialysis; SLED, sustained low-efficiency dialysis; CRRT, continuous renal replacement therapy; PD, peritoneal dialysis.

*For continuous arterio-venous (AV) therapies.
demonstrated adequate solute removal and acceptable hemodynamic tolerability with this technique and showed that systemic anticoagulation could be avoided (35).

**PD**

In the developing world, the availability of CRRT techniques has resulted in a substantial decline in physicians’ expertise with and use of PD for the treatment of AKI, and its use is mainly confined to pediatric patients. Nevertheless, it is also widely used in regions with limited resources because of its ease of use, low cost, and minimal infrastructural requirements. PD has other advantages in that it does not require vascular access or anticoagulation, it does not cause a disequilibrium syndrome, and patients hemodynamically tolerate it relatively well compared with IHD. Disadvantages of PD are its overall lower effectiveness (especially in patients with splanchnic hypoperfusion or who are on vasopressors); risk of protein loss; unpredictability of solute and fluid removal; need for an intact peritoneal cavity; and risks for peritonitis, diaphragmatic splinting leading to ventilatory compromise, and fluctuating blood glucose levels. Recent developments in the technique of PD (use of flexible and cuffed catheters, automatic cycling, and continuous-flow PD) have increased its potential to become an acceptable alternative to other forms of RRT for AKI, but direct comparative effectiveness trials are extremely limited (23).

Current indications for PD in patients with AKI may include bleeding diathesis, hemodynamic instability, and difficulty obtaining vascular access. Extremely high catabolism, severe respiratory failure, severe ileus, intra-abdominal hypertension, recent abdominal surgery, and diaphragmatic peritoneum-pleura connections are contraindications to PD (23).

**KDIGO Guidelines**

Acute renal replacement modality should be chosen according to both technical and clinical issues; patient outcome is more a function of the skill and expertise involving medical and nursing personnel performing the treatment than that of the modality itself (Fig. 1). KDIGO guidelines suggest the following strategies for RRT modality choice (23):

1. **Use continuous and intermittent RRT as complementary therapies in AKI patients. (Not Graded)**
2. **CRRT, rather than standard intermittent RRT, is recommended for hemodynamically unstable patients. (2B)**
3. **CRRT, rather than intermittent RRT, is re-

**Optimal Dosing**

**IHD**

Dosing in IHD is dependent on the dose delivered per session plus the frequency of sessions. Therefore, outcomes may vary according to differences in dose per session as applied to a fixed treatment schedule or differences in treatment schedule as applied to a fixed dose per session. In addition, alterations in the dose per session, as well as in the dialysis schedule, can also be evaluated (24).

No studies have yet evaluated the impact of differences in dose per session in patients undergoing IHD on a fixed schedule (such as three times per week). Some data suggest that dosing may have an impact on patients with intermediate levels of disease severity (24).

The results of the VA/NIM Acute Renal Failure Trial Network (ATN) study showed that if IHD is provided 3 times per week, the minimum delivered Kt/V should be 1.2 per treatment, with the delivered dose of therapy monitored (36). If this minimum dose is achieved, there is no evidence that more frequent hemodialysis is associated with improved outcomes unless it is necessitated for specific acute indications (e.g., hyperkalemia). Surveys of current practice in the United States suggest the delivered dosage of hemodialysis is only infrequently assessed (37).

**CRRT**

The outcomes of a higher dose of CRRT have been assessed in several randomized controlled trials
and in two meta-analyses. Conflicting results related to patient survival have been reported (38-43).

To address the issue of optimal dose in CRRT and IHD, the ATN study (33), the Randomized Evaluation of Normal versus Augmented Level (RENA) Replacement Therapy study (44) and two meta-analyses (43, 45) were performed. All these studies found that higher intensity dialysis did not result in improved survival or clinical benefits compared with standard-intensity dialysis.

Observational studies have suggested that the actual effluent volume delivered during CRRT is substantially less than the prescribed dose. In the Dose Response Multicentre International Collaborative Initiative (DO-RE-MI) study of 338 patients treated with CRRT, for example, the median delivered dose of CRRT was 27 mL·kg⁻¹·h⁻¹ despite of a median prescribed dose of 34.3 mL·kg⁻¹·h⁻¹ (45). In addition, the actual patient time on therapy each day in both ATN (36) and RENAL (44) studies probably exceeded the patient time on therapy achieved in clinical practice, because of enhanced attention to minimizing interruptions in therapy. We therefore suggest that the prescribed dose should exceed the desired delivered dose by a factor of approximately 20% to 25% to adjust for interruptions in study therapy.

**KDIGO Guidelines**

KDIGO guidelines suggest the following strategies for dosage of RRT (23):

1. **The dose of RRT to be delivered should be prescribed before starting each session of RRT.** (Not Graded) Frequent assessment of the actual delivered dose is recommended for adjusting the prescription. (1B)

2. **Provide RRT to achieve the goals of electrolyte, acid-base, solute, and fluid balance that will meet the patient’s needs.** (Not Graded)

3. **Delivering a Kt/V of 3.9 per week is recommended when using intermittent or extended RRT in AKI.** (1A)

4. **Delivering an effluent volume of 20-25 mL/kg/h for CRRT in AKI is recommended.** This will usually require a higher prescription of effluent volume. (Not Graded)

**Discontinuation of Therapy**

RRT is usually continued until the patient shows evidence of recovery of kidney function. Recovery is usually assessed according to empiric data. In oliguric patients, the primary manifestation of recovery of kidney function is increase in UO; however, this finding may not be apparent in patients who are nonoliguric.

Recovery of kidney function may also be manifested by a progressive decline in SCr concentration after the initial attainment of stable values (assessed daily during CRRT or predialysis in patients managed with IHD), despite of a constant dose of renal support. Measurement of creatinine clearance (CCr) is another means of assessing objectively recovery of kidney function (23, 24). In the ATN study, for example, CCr was assessed using 6-h timed urine collections obtained when the UO exceeded 30 mL/h. Because SCr concentration may not be constant during collections, the average concentration can be estimated by measuring SCr at the beginning and end of the timed collection or according to the midpoint CCr concentration. A precise level of kidney function that is needed to allow discontinuation of renal support has not been established; however, a CCr < 12 mL/min is probably inadequate to allow discontinuation of therapy. In the ATN study, renal support was discontinued when the measured CCr exceeded 20 mL/min and was left to the discretion of providers when it was within the range of 12 to 20 mL/min (36).

**Conclusions**

Although many patients with AKI recover sufficient kidney function to be independent of RRT, discontinuation of RRT in AKI has received little attention in the literature. The decision of whether or when to discontinue RRT in a patient with AKI must consider adequate improvement in kidney function to meet demand, improvement in the disorder that prompted kidney support, or futility. It is evident that each of these events is influenced by the initial indication for initiating RRT and is subject to individual variations. The strategy for discontinuing RRT requires consideration of additional factors and often involves a modality transition. KDIGO guidelines suggest the following criteria for discontinuing RRT in AKI (23):

1. **Discontinue RRT when it is no longer required, either because intrinsic kidney function has recovered to the point that it is adequate to meet patient needs, or because RRT is no longer consistent with the goals of care.** (Not Graded)

2. **Use of diuretics is recommended for enhancing kidney function recovery, or reducing the duration or frequency of RRT.** (2B)

There are several areas in the AKI arena where high-quality evidence is lacking. The optimal timing of RRT initiation in AKI remains a critical area of uncertainty. With respect to AKI in the ICU, the funda-
mental principal that guides all medical therapy—do no harm—is especially pertinent.

New classification systems for AKI may enhance standardization of the diagnosis and staging of this clinical syndrome. Novel biomarkers for the early diagnosis of AKI may represent a breakthrough for clinicians if the biomarkers are accurate, reproducible, and applicable in different settings. There are currently no specific therapeutic interventions for patients with established AKI (46, 47).

A well-powered trial is required to examine this issue, which may require an early intervention guided by novel AKI biomarkers. Further trials are required to address the clinical benefits that may be conferred by convective clearance, high cutoff filters, and the bioartificial kidney (48).

### References


