Application of Continuous Renal Replacement Therapy: What Should We Consider Based on Existing Evidence?

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Key Words
Acute kidney injury · Continuous renal replacement therapy · Indication · Prescriptions

Abstract
Background: Continuous renal replacement therapy (CRRT) is performed mainly in patients with acute kidney injury, severe sepsis, or septic shock. Evidence has emerged about the indications for and therapeutic conditions of CRRT. In this review, we focus on the evidence for CRRT to date. Summary: CRRT employs diffusion, convection and adsorption to remove solutes from plasma. Indications can be divided into renal and non-renal indications. Concrete renal indications have not yet been determined, except for life-threatening absolute indications. Modality selection is a point of debate. Intermittent renal replacement therapy is reportedly equivalent to CRRT in terms of overall survival. However, the selection of modality must consider individual circumstances. The optimal dosage of CRRT has proven to be lower than that previously recommended, and the dosage is almost the same as the one employed in the ‘real-world’ setting. Patients treated by CRRT often have bleeding complications. In this situation, regional citrate anticoagulation can be used, but nafamostat is widely used in Japan. The right jugular vein is the most preferred vascular access site because it has the lowest likelihood of catheter malfunction. As for the complications of CRRT, hypophosphatemia and nutrient loss should be managed properly. When CRRT is no longer necessary, we should consider the appropriate timing of discontinuation.

Key Messages: Even though CRRT is an established technique, several points remain under debate. Individualization of therapy should be considered in light of the changes in patient characteristics.

Overview of Continuous Renal Replacement Therapy

Renal replacement therapy (RRT) is the method for replacing failing renal function. Continuous renal replacement therapy (CRRT) is a pivotal treatment strategy for renal failure in the intensive care setting [1]. In addition to the removal of waste products, other molecules such as cytokines are also the target of removal in CRRT, especially in septic patients.

The modalities of CRRT include continuous (veno-venous) hemofiltration (CVVH or CHF), continuous (veno-venous) hemodialysis (CVVHD or CHD), and continuous (veno-venous) hemodiafiltration (CVVHDF or CHDF) [1] (fig. 1). CHD uses diffusion, CHF uses convection, and CHDF uses both. Differences in concentration and transmembrane pressure are the driving force of diffusion and convection, respectively. Substances with a larger molecular weight can be removed through filtration, whereas they can hardly be removed by diffusion. Adsorption is also the mechanism of solute removal of CRRT. It uses physicochemical interaction between the
membrane material and target substances. Polymethyl methacrylate [2, 3] and polyacrylonitrile (specifically AN69™) [4] are two major materials used in adsorption during CRRT.

**Indications of Renal Replacement Therapy**

**Renal Indications**

Although several groups of indications for RRT for acute kidney injury (AKI) have been proposed, definitive indications have not been determined except for life-threatening conditions such as hyperkalemia, severe congestion, profound acidosis, and uremic conditions [5, 6]. A proposal describes the indications from the perspective of absolute or relative indications [6] (table 1). The Kidney Disease Improving Global Outcomes (KDIGO) guideline for AKI also describes the indications for RRT, including renal support [7].

**Timing of Initiation of Renal Replacement Therapy**

Several observational studies demonstrated that, before the era of AKI, patients who started RRT at urea levels of 70–150 mg/dl had better survival than those who...
started at 150–200 mg/dl [8]. In the era of AKI, the definitive timing of initiation based on urea concentration remains controversial. A large prospective cohort study involving 1,238 patients with AKI from 23 countries investigated the relationship between urea levels at initiation or timing and mortality. However, the results were inconsistent in the definitions of timing [9]. Several meta-analyses investigated the influence of timing of RRT initiation on mortality [10–12], and while some of them demonstrated that an ‘early start’ lead to better survival [11, 12], the concrete definitions of ‘early start’ were diverse and definitive conclusions have not been drawn. Therefore, a urea level at 100 mg/dl seems to be a clinically relevant indication for RRT initiation, as some articles and guidelines have proposed [5, 6].

**Selection of Modality: Intermittent, Continuous, or Other?**

Intermittent conventional hemodialysis and CRRT are the major options for RRT in AKI patients. Table 2 shows the characteristics of each modality. CRRT can perform volume reduction continuously with minimal effects on hemodynamics compared with intermittent RRT (IRRT) [13, 14] and it attains volume control more easily [15]. Solute rebound does not occur during the course of CRRT. Thus, peaks in solute levels are seen in IRR but not in CRRT [16–18]. A study reported that brain edema on computed tomography was evident after IRR, while no edema was observed after CRRT because of equilibrated removal of solutes [19]. Thus, CRRT might be more favorable for patients who are prone to elevation of intracranial pressure. CRRT, however, requires larger doses of anticoagulant and is a labor-intensive procedure. In conditions such as hyperkalemia where higher clearance is required, IRR is more favorable than CRRT because of the limited hourly clearance of CRRT.

Many clinical trials have compared the prognoses of patients who underwent IRR or CRRT. To date, however, conclusive evidence of survival benefits has not been shown in randomized controlled trials (RCTs) [15, 20–22] or meta-analyses [13, 23]. Hemodynamic stability was observed in one meta-analysis [13]. From the clinical point of view, patients with unstable hemodynamics or oxygenation who require a large amount of fluid removal might benefit from CRRT. Patients who require removal of larger solutes such as cytokines or myoglobin are also the target group for CRRT.

**Extended Daily Dialysis: The Third Modality**

Extended daily dialysis (EDD) is another modality of choice. This modality utilizes the same machine as IRR. However, the blood and dialysate flow rates are reduced

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**Table 1. Renal indications for renal replacement therapy in acute kidney injury**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Characteristics</th>
<th>Absolute/Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic abnormality</td>
<td>BUN &gt;76 mg/dl (27 mmol/l)</td>
<td>Relative</td>
</tr>
<tr>
<td></td>
<td>BUN &gt;100 mg/dl (35.7 mmol/l)</td>
<td>Absolute</td>
</tr>
<tr>
<td></td>
<td>Hyperkalemia &gt;6 mEq/l</td>
<td>Relative</td>
</tr>
<tr>
<td></td>
<td>Hyperkalemia &gt;6 mEq/l with ECG abnormalities</td>
<td>Absolute</td>
</tr>
<tr>
<td></td>
<td>Dysnatremia</td>
<td>Relative</td>
</tr>
<tr>
<td></td>
<td>Hypermagnesemia &gt;8 mEq/l (4 mmol/l)</td>
<td>Relative</td>
</tr>
<tr>
<td></td>
<td>Hypermagnesemia &gt;8 mEq/l (4 mmol/l) with anuria and absent deep tendon reflexes</td>
<td>Absolute</td>
</tr>
<tr>
<td>Acidosis</td>
<td>pH &gt;7.15</td>
<td>Relative</td>
</tr>
<tr>
<td></td>
<td>pH &lt;7.15</td>
<td>Absolute</td>
</tr>
<tr>
<td></td>
<td>Lactic acidosis related to metformin use</td>
<td>Absolute</td>
</tr>
<tr>
<td>Anuria/oliguria</td>
<td>RIFLE class R</td>
<td>Relative</td>
</tr>
<tr>
<td></td>
<td>RIFLE class I</td>
<td>Relative</td>
</tr>
<tr>
<td></td>
<td>RIFLE class F</td>
<td>Relative</td>
</tr>
<tr>
<td>Fluid overload</td>
<td>Diuretic sensitive</td>
<td>Relative</td>
</tr>
<tr>
<td></td>
<td>Diuretic resistant</td>
<td>Absolute</td>
</tr>
</tbody>
</table>

From Gibney et al. [6]. The proposed indications for renal replacement therapy are categorized as either absolute (life-threatening) or relative indications. BUN = Blood urea nitrogen.
and treatment time is prolonged [24]. Patients treated by EDD attained volume control that was comparable with CRRT, although those treated by EDD experienced lower blood pressure because of the higher rate of fluid reduction [25]. Solute removal is equivalent between EDD and CRRT [26–28]. A smaller amount of anticoagulation was required in EDD than in CRRT [27]. A meta-analysis comparing the two modalities demonstrated similar survival [29].

Non-Renal Indications

CRRT potentially removes larger solutes such as cytokines by means of convection or adsorption. The AN69 membrane was shown to adsorb cytokines [4, 30], including high mobility group box 1 [30]. The group at Chiba University has extensively demonstrated that the polymethyl methacrylate membrane reduces the levels of plasma cytokines by adsorption and improves clinical outcomes in conditions with hypercytokinemia [2, 3].

Removal of cytokines by the CRRT hemofilter has been demonstrated [31–33]. On the other hand, the effects of CRRT on the plasma level of cytokines are controversial; some studies demonstrated their reduction [34, 35], while others did not [32, 36]. It is hypothesized that the peak concentrations of cytokines are crucial in organ injury and it is beneficial to cap their levels by CRRT (peak concentration hypothesis) [37].

### Table 2. Comparison of intermittent and continuous renal replacement therapy

<table>
<thead>
<tr>
<th></th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Continuous renal replacement therapy (CRRT) | Slow fluid removal  
Minimum effects on hemodynamics  
Large amount of fluid can be eliminated  
Removal of larger solutes (myoglobin, cytokines)  
No rebound in plasma concentration | Continuous anticoagulation  
Increases risks of bleeding  
Higher costs and labor-intense  
Lower clearance  
Requires longer time until attainment of target concentration range  
Continuous therapy; patients are required to stay in bed |
| Intermittent renal replacement therapy (IRRT) | Limited doses of anticoagulation  
Limited risks of bleeding  
Same technique as maintenance hemodialysis  
Lower costs and less labor intensive  
Higher clearance  
Rapid control of life-threatening hyperkalemia  
Off-time of renal replacement is intended to enhance the physical activity of the patient | Intermittent therapy  
Larger fluid removal rate  
Prone to hemodynamics disturbance  
Rebound of concentrations during the course; fluctuation of levels of solutes is inevitable  
Limited clearance of larger solutes |

### Prescription of Continuous Renal Replacement Therapy

#### Dose of Continuous Renal Replacement Therapy

Solute removal in CRRT is achieved by diffusion, convection, and adsorption. The efficacy of diffusion or convection can be modified by adjusting the dialysate flow rate and ultrafiltration rate, respectively. Clearance of small solutes by diffusion is determined by the dialysate flow rate, and it is almost equal to the flow rate in usual conditions [38]. On the other hand, the clearance of small molecules by convection is equal to the ultrafiltration rate [38]. Thus, the clearance attained by CHDF is theoretically equal to the sum of dialysate flow rate and ultrafiltration rate, respectively. Clinical trials have therefore utilized the effluent flow rate in their assessments. However, there are concerns that the effluent volume is not necessarily equal to actual clearance [39, 40]. Moreover, the length of time of discontinuation of therapy is considerable, mainly due to clotting of the circuit. Such ‘down time’ is also an issue that reduces the actual dose of CRRT [39].

#### Evidence on Continuous Renal Replacement Therapy Doses

In 2000, Ronco et al. [41] published epoch-making evidence that higher effluent volume, as much as 35 or 45 ml/kg/h, was associated with better survival among patients with acute renal failure. This was bolstered by sub-
sequent studies demonstrating that similar [42] or even higher [43] doses of CRRT were associated with better prognosis in such patients. However, registry data from 23 countries demonstrated that the median effluent flow rate was 20.4 ml/kg/h [44]. Data from 34 intensive care units in Australia and New Zealand demonstrated similar results, with typical urea clearance of 24.3 ml/kg/h [45]. Discrepancies between evidence and ‘real-world’ practice have become evident. Thereafter, several observational studies [46] and RCTs [47] found that intense CRRT (>35 ml/kg/h [46] or 72 liters/day [47]) does not necessarily result in better prognoses. RCTs were conducted to compare the doses of CRRT in terms of patient survival [48–50]. One compared 20 and 35 ml/kg/h in 200 critically ill patients [48]. The VA/NIH Acute Renal Failure Trial compared 20 and 35 ml/kg/h in 1,124 AKI patients with at least one non-renal organ failure or sepsis [49]. The most recent study is RENAL Replacement Therapy Study that compared 25 and 40 ml/kg/h in 1,508 patients [50]. All of the trials demonstrated that the ‘lower’ doses and the ‘higher’ doses were equivalent in terms of patient survival. Therefore, the disparity between evidence and ‘real-world’ practice was resolved.

In Japan, the maximum volume of supplementary fluid that can be used per day is determined by the government healthcare reimbursement system, which is as low as 15–20 liters/day (the volume differs depending on prefecture). Data from questionnaire surveys revealed a median effluent volume of 16 ml/kg/h in Japan. However, survival was better than that predicted from acute physiology and chronic health evaluation II (APACHE II) score [51].

**Anticoagulation**

Blood purification therapy usually requires anti-coagulation. Unfractionated heparin is widely used for this purpose, and is also used in CRRT [44]. However, anti-coagulation potentially causes bleeding complications. Regional citrate anticoagulation (RCA) is used for bleeding diathesis or heparin-induced thrombocytopenia. RCA reportedly showed non-inferiority [52, 53] or even favorable results [54] compared with heparin in terms of filter life. Moreover, clinical studies [52–54] consistently indicated that RCA was associated with a lower incidence of bleeding complications. Therefore, the KDIGO guideline recommends RCA as the first-line anti-coagulant in patients with bleeding complications [7].

Hirudin, a low molecular weight heparin (LMWH), and nafamostat are other anti-coagulants that are being investigated or used for CRRT. Hirudin is a recombinant peptide that is degraded in the kidneys and reportedly has a markedly prolonged half-life in patients with renal failure [55]. Therefore, this agent has a very limited indication and does not seem appropriate for CRRT anticoagulation. One trial compared LMWH with unfractionated heparin in CRRT and found comparable results, but the cost of the LMWH is higher than that of unfractionated heparin [56]. Nafamostat is a synthetic serine protease inhibitor commonly used in Japan and Korea. The drug inhibits the activity of a range of coagulation factors and acts as an anti-coagulant [57]. Its half-life is short (alpha phase 1.1 min and beta phase 23.1 min based on manufacturer data) and it is eliminated by dialysis because of its small molecular weight (539.6). Therefore, this anticoagulant is not expected to exacerbate bleeding. Evidence from both observational [58] and interventional [59, 60] studies have demonstrated its utility in CRRT.

**Vascular Access**

Placement of vascular access is another crucial step in blood purification therapy. Non-cuffed temporary catheter is usually preferred for vascular access. Options exist with regard to the insertion site and length of catheters. One study of 736 patients compared insertion sites in terms of catheter malfunction and the dosage of RRT. Compared with femoral veins, the right jugular vein was associated with a lower incidence of malfunction while the left jugular vein was associated with a higher incidence [61]. Another study demonstrated that the femoral vein was significantly associated with infectious complications, especially in heavier (>90 kg) patients [62]. Therefore, the KDIGO guideline recommends the following order of preference of insertion site: the right jugular vein, femoral vein, left jugular vein, and subclavian vein, with preference for the dominant side for preparation of future permanent vascular access for maintenance dialysis [7].

**Adverse Events and Adjunctive Therapies**

**Electrolyte Disorders**

Hypophosphatemia is one of the major complications of CRRT. Post-hoc analysis of the RENAL study demonstrated that 32.1% of patients had hypophosphatemia <0.6 mmol/l. The incidence was highest 2–3 days after initiation of CRRT and the overall incidence was 58 episodes per 1,000 patient-days for the lower dose, while it was 112 episodes per 1,000 patient-days for the higher dose. Multivariate analysis also demonstrated that the higher dose was significantly associated with hypophos-
Nutrition

The target of RRT is small, water-soluble molecules. Therefore, many nutrients including both macronutrients and micronutrients are removed during RRT. One of the most clinically important issues is the removal of amino acids including glutenine. ESPEN guidelines or other articles recommend larger amounts of protein intake (>1.5 g/kg/day [64], 1.5–1.8 g/kg/day [65, 66], or even 1.5–2.0 g/kg/day [67]). Micronutrients are also removed through CRRT treatments. One article recommended supplementation of thiamin (100 mg/day), vitamin C (250 mg/day), and selenium (100 μg/day) [65].

Discontinuation of Continuous Renal Replacement Therapy

Discontinuation or transition to maintenance intermittent hemodialysis should be considered at an appropriate time because of the nature of CRRT. When conditions that require continuous treatment no longer exist, the transition to IRRT must be considered. On the other hand, sufficient urinary output and a spontaneous fall in creatinine without a change in the prescription of RRT are signs that prompt us to consider discontinuing RRT. Urinary volume >400 ml/day without diuretics or >2,300 ml/day with diuretics have been demonstrated to be good indicators for the discontinuation of CRRT [68].

Conflicts of Interest

The author declares no conflicts of interest or financial support in relation to this article.


