

Renal Replacement Therapy for Acute Kidney Injury

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Key Words

Acute kidney injury · Biomarkers · Continuous renal replacement therapy · Intermittent hemodialysis · Sustained low-efficiency dialysis · Dialysis dose

Abstract

The treatment of established acute kidney injury (AKI) is largely supportive in nature. Renal replacement therapy remains the cornerstone of management for the minority of patients who have severe AKI. Optimization of renal replacement therapy may modulate the high mortality associated with AKI. Recent trials indicated that continuous renal replacement therapy does not confer a survival advantage as compared to intermittent hemodialysis. Furthermore, there is no evidence to support a more intensive strategy of renal replacement therapy in the setting of AKI. There is comparatively limited data regarding the ideal timing of renal replacement therapy initiation and the preferred mode of solute clearance.

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Introduction

Acute kidney injury (AKI) is a frequent complication of hospitalization that is associated with substantial morbidity, mortality and health care expenditures [1, 2]. There is significant variability in the reported prevalence (1–25%) and mortality (20–60%) associated with AKI in

hospitalized patients. This is to some extent related to the lack of a uniform definition for AKI. Two classification systems have emerged that may serve to unify communication concerning AKI (table 1) [3, 4]. The RIFLE classification system was formulated by the Acute Dialysis Quality Initiative and defines three strata of increasing severity of AKI: Risk, Injury and Failure, based on relative changes in serum creatinine and urine output, and two outcome strata (Loss and End-stage renal failure) [5]. The three-stage Acute Kidney Injury Network classification system largely overlaps with the three first stages of RIFLE, with the addition of an absolute serum creatinine increase of 0.3 mg/dl to qualify for stage 1, a limit on the time interval for the creatinine rise to 48 h, and categorization of patients started on renal replacement therapy (RRT) as stage 3 regardless of creatinine or urine output. In both classification systems, escalating severity of AKI is associated with incrementally worse outcomes [6].

Although understanding of the epidemiology of AKI has improved, there are no proven therapies that reverse the course of established AKI. RRT is a key component of the supportive care given to patients with severe AKI. Approximately 4% of all critically ill patients will require RRT [7]. Among RRT-requiring patients who survive the critical phase of their illness, the majority will be free of RRT at the time of hospital discharge [7, 8]. This review will discuss novel diagnostic strategies for AKI but will focus on the management of AKI, with an emphasis on renal replacement strategies.

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Table 1. The Acute Dialysis Quality Initiative and Acute Kidney Injury Network classification systems for AKI

Stage	Serum creatinine change	Urine output criteria
<i>Acute Dialysis Quality Initiative RIFLE criteria [4, 5]</i>		
Risk	increase in serum creatinine of 1.5–2 times baseline	less than 0.5 ml/kg/h for more than 6 h
Injury	increase in serum creatinine of 2–3 times baseline	less than 0.5 ml/kg/h for more than 12 h
Failure	increase in serum creatinine of >3 times baseline OR if baseline creatinine >4 mg/dl, any 0.5 mg/dl increase qualifies	less than 0.3 ml/kg/h for more than 24 h OR anuria for >12 h
Loss	persistent need for RRT for >4 weeks	
End-stage	persistent need for RRT for >3 months	
<i>Acute Kidney Injury Network criteria</i>		
1	increase in serum creatinine of 1.5–2 times baseline OR 0.3 mg/dl increase from baseline	less than 0.5 ml/kg/h for more than 6 h
2	increase in serum creatinine of 2–3 times baseline	less than 0.5 ml/kg/h for more than 12 h
3	increase in serum creatinine of >3 times baseline OR if baseline creatinine >4 mg/dl, any 0.5 mg/dl increase qualifies OR if any RRT given	less than 0.3 ml/kg/h for more than 24 h OR anuria for >12 h

New Biomarkers in AKI

Current diagnostic paradigms for AKI are limited by reliance on serum creatinine, which is affected by age, gender and muscle mass. In addition, elevations in serum creatinine may occur several days after the actual injury. The search for AKI biomarkers has focused on identifying alternatives to serum creatinine. Urinary neutrophil gelatinase-associated lipocalin (NGAL) and interleukin-18 may provide insights into the cause of AKI [9, 10]. Similarly, urinary and serum NGAL, serum cystatin C and urinary kidney injury molecule-1 (KIM-1) may facilitate the early diagnosis of AKI. KIM-1 also shows promise in predicting adverse events in patients with established AKI [11]. Ongoing studies are clarifying the role of these biomarkers in larger patient cohorts. Ultimately, it will need to be shown that integration of novel biomarkers into clinical decision-making impacts on patient-relevant outcomes.

Pharmacological Treatment of AKI

Pharmacological interventions in AKI have targeted the prevention of renal ischemia or modulation of the ensuing inflammatory or hormonal milieu. Low-dose dopamine, historically thought to improve renal perfusion and thus prevent AKI, has recently been shown in a meta-analysis to have no effect on mortality and RRT requirement [12]. Similarly, atrial natriuretic peptide (ANP), a vasoactive endogenous hormone that increases glomerular filtration by dilating afferent and constricting efferent

arterioles, was felt to be a promising therapeutic option. Anaritide, an ANP analogue, was initially shown to have no effect on dialysis-free survival and caused increased rates of hypotension in a randomized controlled trial (RCT) of AKI of variable etiology when given at a dose of 200 ng/kg/min [13]. However, in a small randomized study of 59 postcardiac surgery patients with AKI, anaritide at a lower dose (50 ng/kg/min) was found to significantly increase the rate of 21-day dialysis-free survival [14]. A recent meta-analysis of 19 different RCTs showed a trend towards reduction of RRT requirement when ANP was used in the prevention of AKI, however an overall increase in mortality was observed when ANP was used in the treatment of established AKI (particularly with higher doses) [15].

Recombinant human insulin-like growth factor 1 showed encouraging results at reducing renal tubular apoptosis and inflammation in mice when administered immediately after renal ischemia [16]. In a small RCT of 72 critically ill patients with AKI, insulin-like growth factor 1 failed to show any benefit [17]. More recently, N-acetylcysteine and sodium bicarbonate have received a great deal of attention in the setting of contrast nephropathy and postcardiac surgery AKI prevention [18, 19]. The clinical benefits of these interventions remain controversial.

There are a number of other agents in preclinical studies that show promise in the prevention or early treatment of AKI. However, the efficacy of these therapies in clinical practice may depend on the early identification of AKI [20].

Table 2. Practical comparison of acute RRT modalities

	Intermittent hemodialysis	Sustained low-efficiency dialysis	Continuous renal replacement therapy
Session duration, h	3–5	8–12	24
Blood flow, ml/min	300–400	200–300	100–200
Dialysate flow, ml/min	500–800	200–350	25–40
Anticoagulation requirement	heparin or none	heparin or none	heparin or regional citrate

Table 3. Results of individual RCTs comparing CRRT to IHD

Study	Sample size		Primary endpoint	Mortality, %		Persistent dialysis requirement ^a , %	
	CRRT	IHD		CRRT	IHD	CRRT	IHD
Mehta et al. [21]	84	82	ICU mortality	59.5	41.5	14.0	7.0
Augustine et al. [23]	40	40	in-hospital mortality	67.5	70.0	61.5	66.7
Uehlinger et al. [24]	70	55	in-hospital mortality	47.0	51.0	2.7	3.7
Vinsonneau et al. [22]	175	184	60-day mortality	67.4	68.5	1.8	0.0
Lins et al. [25]	172	144	in-hospital mortality	58.1	62.5	16.9 ^b	25.5 ^b

^a Defined as dialysis dependence at the time of hospital discharge among survivors.

^b Glomerular filtration rate <15 ml/min at the time of hospital discharge.

RRT Modality Choice

Intermittent hemodialysis (IHD), continuous renal replacement therapies (CRRT) and sustained low-efficiency dialysis (SLED) are the principal RRT modalities that are used in the acute setting. Although institutional policies may determine the local availability of these modalities, CRRT and SLED tend to be used in patients with greater hemodynamic instability. There is likely substantial intercenter variability with respect to how each of these forms of RRT is utilized and prescribed.

IHD is typically administered with conventional dialysis machinery that is used in the chronic dialysis population with session length ranging from 3 to 5 h. CRRT is applied with an intended treatment time of 24 h and generally requires dedicated machines that operate at comparatively lower blood and dialysate pump speeds. CRRT may be administered as hemodialysis (continuous venovenous hemodialysis, CVVHD), hemofiltration (continuous venovenous hemofiltration, CVVH) or a combination of these (continuous venovenous hemodiafiltration, CVVHDF). SLED, sometimes referred to as extended dialysis, is considered a 'hybrid' of IHD and

CRRT. SLED is administered using conventional dialysis technology but typical sessions run for 8–12 h using blood and dialysis flows that are intermediate to those prescribed in IHD and CRRT. Table 2 summarizes the differences between these three modalities.

CRRT versus IHD

Most trials that addressed the question of optimal RRT modality compared CRRT and IHD (table 3). A trial by Mehta et al. [21] revealed higher ICU mortality in patients treated with CRRT as compared to IHD (59.5 vs. 41.5%). This finding was tempered by apparent baseline imbalances between the groups, whereby patients randomized to CRRT had a greater severity of illness. Renal recovery did not differ between the groups.

In a larger multicenter RCT conducted in France comparing CRRT and IHD in critically ill patients with AKI [22], 60-day mortality was not reduced by CRRT, and there was no significant difference in the duration of RRT dependence. Three additional trials have shown no survival benefit with CRRT [23–25].

The presumption of greater hemodynamic stability with CRRT also remains controversial. Three RCTs sug-

gested no advantage with CRRT as compared to IHD [22, 24, 26], while others demonstrated more favorable hemodynamics with CRRT [23, 27]. Even if CRRT confers a hemodynamic benefit, it is unclear whether this translates into improvements in the patient-relevant outcomes of survival and renal recovery.

CRRT versus SLED

In addition to the absence of a survival advantage, CRRT is more costly than IHD and is associated with a number of obstacles such as continuous patient immobilization, the requirement for anticoagulation and the need for specialized machines and premixed commercial solutions [28]. This has stimulated a search for a strategy that incorporates 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 [29, 30]. However, only two small RCTs have compared SLED and CRRT [31, 32]. Kielstein et al. [31] randomized 39 critically ill patients with AKI to receive either 24 h of CVVH or 12 h of SLED. Using invasive monitoring, these authors found no significant differences in all measured hemodynamic parameters (mean arterial pressure, systemic vascular resistance, cardiac output) with comparable removal of creatinine and urea. A smaller study randomized 16 patients to receive three sessions with either CVVH or SLED (with an added hemofiltration component), and showed that fluid removal and hemodynamic parameters were similar in both groups [32]. Although these preliminary data suggest that SLED may supplant CRRT as the modality of choice for hemodynamically unstable patients with AKI, further studies that utilize patient-relevant outcomes are required to define the precise role of SLED.

A strategy has recently been described whereby CRRT machinery was applied over a contracted treatment time of 9 h, using increased blood and effluent flow rates. Termed accelerated venovenous hemofiltration, this modality retains many of the feasibility advantages of SLED, but dedicated commercial solutions were still required. A retrospective case series demonstrated adequate solute removal, acceptable hemodynamic tolerability and the ability to avoid systemic anticoagulation [33].

Intensity of RRT

The impact of RRT intensity or dose on patient outcomes has been a matter of controversy. Most definitions of acute RRT dose are based on small molecule removal, as exemplified by urea, while ignoring other crucial aspects of RRT adequacy in AKI, such as volume and electrolyte control. Furthermore, assumptions pertaining to urea kinetic modeling that are applied to end-stage renal disease are inappropriate in the acute setting. Finally, many of the benefits derived from acute RRT may relate to large-molecular-weight solute clearance, which is poorly quantified.

Schiffl et al. [34] compared daily to thrice-weekly IHD in 146 critically ill patients with AKI. Patients receiving daily hemodialysis had significantly lower mortality as compared to those receiving alternate-day dialysis (28 vs. 46%) and a shorter time to renal recovery, as defined by independence from dialysis (mean of 9 vs. 16 days). The study was designed to provide a minimum Kt/V_{urea} of 1.2 for each treatment session in both arms of the study. However, the authors demonstrated that the actual delivered dose per session was significantly lower than intended, albeit similar in both arms of the study (mean Kt/V_{urea} of 0.92 vs. 0.94). It is therefore unclear if the survival benefit demonstrated in this study was mediated by the mere provision of an adequate dialysis dose in the daily dialysis arm or by the true merits of more intensive therapy.

Ronco et al. [35] randomized 425 critically ill patients with AKI to continuous hemofiltration rates of 20, 35 or 45 ml/kg/h. They showed enhanced survival at 15 days following discontinuation of RRT in the two high-dose groups when compared to the low-dose group. The benefits of high-intensity CRRT were also seen in a trial by Saudan et al. [36] who compared CVVH (mean effluent flow of 25 ml/kg/h) with CVVHDF (mean effluent flow of 42 ml/kg/h) in 206 critically ill patients. Ninety-day survival was significantly higher among patients treated with CVVHDF as compared with CVVH (59 vs. 34%). These results contrasted with two other trials demonstrating no benefit with intensified therapy [37, 38].

In the recently completed Veterans Administration/National Institutes of Health Acute Renal Failure Trial Network (ATN) study, over 1,100 critically ill patients with AKI requiring RRT were randomized to an intensive or a less intensive treatment strategy [39]. In the intensive arm, hemodynamically unstable patients received CRRT at 35 ml/kg/h or 6 sessions per week of SLED; if patients were hemodynamically stable, IHD was admin-

istered 6 times per week. In the less intensive arm, hemodynamically unstable patients received CRRT at 20 ml/kg/h or thrice-weekly SLED; stable patients received thrice-weekly IHD. Patients were able to shift between RRT modalities depending on their evolving hemodynamic status, thereby reflecting usual clinical practice. The trial was well executed with minimal crossover and excellent follow-up. Sixty-day mortality was 53.6 and 51.8% in the intensive and less intensive arms, respectively (NS). There were no appreciable differences in renal recovery.

Two important limitations of the ATN study should be considered. In both treatment arms, CRRT was delivered as an equal mix of hemodialysis and hemofiltration. The benefits of more intensive RRT may be conferred by the latter component, and it is notable that hemofiltration was administered exclusively in the positive trial by Ronco et al. [35]. The generalizability of the ATN study is also limited by the exclusion of patients with significant pre-morbid chronic kidney disease, a population that comprises a large proportion of AKI patients seen in clinical practice [7, 40]. The Randomised Evaluation of Normal vs. Augmented Level (RENAL) Replacement Therapy study (ClinicalTrials.gov identifier NCT00221013) enrolled 1,500 critically ill patients in Australia and New Zealand with AKI at multiple sites. Preliminary study results have been reported (although not published to date) and indicate that CVVHDF at a dose of 40 ml/kg/h did not confer improved 90-day survival as compared to a dose of 25 ml/kg/h.

Timing of RRT Initiation

Conventional indications for RRT initiation in AKI include refractory hyperkalemia, severe metabolic acidosis, hypervolemia, and uremic end-organ complications. However, one or more of these indications may emerge well after the time of the kidney insult. The resulting delay in initiating RRT may prolong patient exposure to the uncorrected metabolic effects of kidney failure, which may in turn contribute to adverse outcomes.

There is a very limited evidence base to guide the timing of RRT initiation in AKI. A recent meta-analysis identified 23 relevant studies and found a wide array of study designs and definitions for 'early' and 'late' RRT initiation [41]. In the 5 RCTs that addressed this issue, early initiation of RRT was associated with a trend towards mortality reduction [risk ratio (RR) 0.64, 95% confidence interval (CI) 0.40–1.05] and in the 18 observa-

tional studies, a mortality risk reduction of 28% (RR 0.72, 95% CI 0.64–0.82) was observed. It is noteworthy that all of the RCTs cited in the meta-analysis had small sample sizes and were generally of poor quality.

Defining the optimal timing of RRT initiation in AKI remains a research priority. Prior to embarking on a definitive RCT, substantial preliminary work will be required to determine the prevailing standard of care in the timing of RRT initiation. This should set the parameters for the control arm in such a trial. An 'early start' strategy could then be derived relative to the standard of care.

Convection and Removal of Large-Molecular-Weight Solutes

Convection, as provided through hemofiltration, and diffusion, as provided through hemodialysis, are the principal modes of solute removal in AKI. Convection utilizes hydrostatic pressure to effect the translocation of water across the semi-permeable membrane while concomitantly dragging solutes with molecular weights that are below the pore size of the membrane. Diffusion fuels the movement of solutes across a semi-permeable membrane down concentration gradients for the respective solutes. Both modes provide reliable clearance of low-molecular-weight molecules such as urea, whereas larger-molecular-weight solutes are more effectively removed by convection. Large molecules of particular interest include inflammatory cytokines such as tumor necrosis factor- α and interleukin-6 that may serve as key mediators in the pathogenesis of AKI. Despite the conceptual appeal of convective clearance, there is a paucity of patient-level data on the optimal mode of clearance in AKI resulting in a great deal of practice variability. A small RCT evaluated outcomes of 20 patients who received CVVH versus CVVHD. There were no significant differences in mortality, renal recovery or duration of ICU stay [42].

Removal of large-molecular-weight solutes may also be enhanced by the use of hemodiafilters with larger pore sizes. These so-called high cutoff hemodiafilters have pores of 50–60 kDa (as compared to 20–30 kDa for conventional hemodiafilters), thereby enabling the translocation of larger-sized inflammatory mediators. Haase et al. [43] recently completed a double-blind crossover RCT of 10 septic patients with AKI who received 4-hour sessions of hemodialysis with a high cutoff dialyzer and a standard high-flux dialyzer, respectively, in random se-

quence. Interleukin-6, interleukin-8 and interleukin-10 concentrations were significantly reduced following therapy with the high cutoff dialyzers with little change in these markers following treatment with the high-flux dialyzer. Similar small solute control was achieved with both dialyzers. Although the clinical implications of these findings need further clarification, other work done by this group suggested improved hemodynamic control in patients treated with a high cutoff hemodiafilter [44].

Renal Tubule Cell Therapy

Contemporary RRT devices are designed to replace the filtration component of kidney function but tubular function is not addressed. Humes et al. [45] have developed a bioartificial kidney known as a renal assist device (RAD), composed of sheets of human tubular cells that are housed within a high-flux hemodiafilter. Preliminary data indicated that these cells successfully performed many of the transport and endocrinologic functions normally attributed to the renal tubular epithelium [46]. A phase II RCT of 58 critically ill patients with AKI compared 72 h of continuous treatment with the RAD and a conventional filter (in series with each other) versus conventional CRRT [47]. Treatment with the RAD was found to be safe with a trend towards reduced mortality at 28 days (33 vs. 61% in patients treated with conventional CRRT). The RR of death in the RAD group, adjusted for comorbid illness, was 0.48 (95% CI = 0.23–0.99). In addition, higher rates of renal recovery were seen in patients treated with the RAD. It should be noted that only 10 of the 40 patients treated with RAD completed the planned 72 h of therapy.

Conclusions

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

It is possible that optimization of the RRT prescription will impact on patient outcomes. Recently completed RCTs have provided clinicians with guidance on some aspects of the RRT prescription but several areas remain unclear. Despite the conceptual advantages of CRRT, multiple RCTs have shown no evidence of improved patient outcomes with this modality, as compared to conventional IHD. The logistic challenges associated with CRRT and the relatively high costs of this modality may stimulate the increased use of SLED. However, well-designed RCTs are still needed to better characterize the reported benefits of SLED prior to its widespread adoption. Recent data have also clarified important questions regarding RRT intensity in AKI. The current balance of evidence suggests that among hemodynamically unstable patients, CRRT need not be administered at doses higher than 20 ml/kg/h, and in more stable patients, alternate-day IHD is acceptable.

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

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Editorial Comment

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This excellent review by Fieghen, Wald and Jaber from Toronto and Boston highlights recent advances in the classification of AKI whilst drawing attention to the limitations of clinical trials in the field. It also brings to the reader's awareness the recent interest in the predictive value of a number of biomarkers including NGAL, IL-18 and KIM-1. These biomarkers have been put forward as early diagnostic and prognostic indicators in AKI.

More recently, Jaber's group in Boston has reported on the influence of patients' genotype on outcomes in AKI. They noted a relationship to adverse outcome of a non-synonymous polymorphism in the coding region of the HIF-1 α gene where a C to T substitution occurs at position +85 in exon 12 [Kolyada et al., 2009]. This association warrants further investigation.

In their minireview, the authors thoroughly and critically review a number of clinical trials of pharmacological interventions as well as those based on replacement therapy modalities or intensity in AKI. Most of these in-

tervention trials are negative as they fail to show significant advantage. This may be due in part to the fact that clinical trials in AKI are very difficult to conduct due to the heterogeneity of the patients involved and associated comorbidities.

Recent interest has also emerged in the impact AKI may have on the incidence of chronic kidney disease as well as on the acceleration of the progression of established chronic kidney disease to end-stage renal disease. This is likely to be particularly relevant in the elderly whose recovery from AKI is often limited and may precipitate end-stage renal disease.

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