

# Renal Replacement Therapy in Acute Kidney Injury: Review



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**Abbreviations:** AKI: Acute Kidney Injury; GFR: Glomerular Filtration Rate; ADQI: Acute Dialysis Quality Initiative; AKIN: Acute Kidney Injury Network; KDIGO: Kidney Disease: Improving Global Outcomes; MOF: Multiple Organ Failure; ICU: Intensive Care Unit; RRT: Renal Replacement Therapy; IHD: Intermittent Hemodialysis; CRRT: Continuous Renal Replacement Therapy; SLED: Sustained Low-Efficiency Dialysis; CVVH: Continuous Venovenous Hemofiltration; CVVHF: Continuous Venovenous Hemodiafiltration; SIRS: Systemic Inflammatory Response Syndrome

## Introduction

Acute kidney injury (AKI) is the abrupt loss of kidney function defined by a rapid (over hours to days) decline in the glomerular filtration rate (GFR) resulting in the retention of metabolic nitrogenous waste products and dysregulation of fluid, electrolyte, and acid-base homeostasis [1]. In 2002, the Acute Dialysis Quality Initiative (ADQI) Group proposed the first consensus definition of AKI. The ADQI work group proposed a classification scheme with three grades based on the magnitude of the increase in serum creatinine level and/or decrease in urine output. The change in serum creatinine was specified as occurring over not more than seven days. Conceptually, the lower grade would provide the greatest sensitivity for diagnosing AKI, whereas the higher grade would provide increasing specificity of diagnosis. These three grades were combined with two outcome stages defined by the need for and duration of renal replacement therapy, which resulted in the five-tiered RIFLE classification (Risk of renal dysfunction, Injury to the kidney, and Failure of kidney function, as well as the two outcome stages, Loss of kidney function and End-stage kidney disease) [2]. More recently, the Acute Kidney Injury Network (AKIN) proposed a modification of the RIFLE classification that includes the Risk, Injury, and Failure criteria with the addition of a 0.3mg/dL or higher increase in the serum creatinine level with 48 hours to the criterion that define Risk [3]. This modification was aimed to increase the sensitivity by including less severe AKI, to impose a time constraint of 48 hours and also to allow for correction of volume status and obstructive causes of AKI. Finally, Kidney Disease: improving global outcomes (KDIGO) proposed a consensus definition utilizing 48hours time frame from AKIN

for an absolute increase in serum creatinine of 0.3mg/dl and 7 days time frame for relative 50% increase in serum creatinine above baseline. Although these criteria are quite useful in epidemiological studies; their clinical utility is uncertain. It seems that these criteria will eventually be replaced to some extent by novel biomarkers of kidney injury and modifications in future will see beyond the horizons of increase in serum creatinine and/or decrease in urine output.

Acute Kidney Injury besides being prevalent is also associated with significant morbidity and mortality. There has been a significant change in the spectrum of severe Acute Kidney Injury (AKI) such that it is no longer mostly a single organ phenomenon but heterogeneous clinical syndrome. Isolated severe AKI is now uncommon where as AKI associated with multi organ failure is the rule, with 80 per cent of cases now associated with multiple organ failure (MOF). The significance of this epidemiological shift is that, despite great advances in renal replacement technique, mortality from AKI, when part of MOF, remains over 50% [4]. The changing nature of AKI requires a new approach using the new advanced technology.

There is no treatment till date to treat AKI per se. In many cases of AKI, correction of underlying problems may allow recovery, but in a substantial fraction of patients, particularly those patients in intensive care units (ICUs) who frequently have additional clinical problems recovery is less certain and there is a requirement for continuing support with Renal Replacement Therapy (RRT). AKI requiring RRT is severe type of AKI [5,6] which is frequently a serious complication of critical illness.

Acute Kidney Injury requiring renal replacement therapy (RRT) occurs in 5-6% of the critically ill patients and is associated with high mortality and significant health care resource utilization [7]. The optimal timing for RRT initiation in AKI remains a matter of debate. Presently, there is no universally accepted consensus regarding when to initiate RRT in patients with AKI. Guidelines recommend that RRT should be initiated in patients who present with life-threatening changes in fluid, electrolytes and acid-base balance; and hence refractory hyperkalemia, severe metabolic acidosis, volume overload, oliguria, overt uremic symptoms, and medication intoxication are all traditionally considered to be classic indications for RRT [2,3].

The ideal RRT should mimic the functions and physiological mechanisms of the native organ, ensuring qualitative and quantitative blood purification, be free of complications, have good clinical tolerance and restore and maintain homeostasis, thus favoring organ recovery. The use of hemodialysis as a treatment for AKI first was introduced successfully by Willem Kolff in the late 1940s and began to be used more systematically in the treatment of military casualties during the Korean War. This resulted in an overall reduction in mortality, from 90% to approximately 50% [8,9]. Although circumstantial, this remains the best evidence to date that dialysis improves outcomes for critically ill patients with AKI [10].

Multiple modalities of Renal Replacement Therapy are available for the management of patients with AKI, including conventional intermittent hemodialysis (IHD), peritoneal dialysis, multiple forms of continuous renal replacement therapy (CRRT), and "hybrid" therapies such as sustained low-efficiency dialysis (SLED). In Intermittent Hemodialysis removal of fluid, solutes and toxins is achieved typically through a dual venous access, over a period of three to five hours, three to seven times weekly. Solute removal is achieved by diffusion and is rapid and efficient [11]. Rapid fluid removal during IHD has been suggested to lead to intra dialytic hypotension, with the potential for further renal injury and prolongation of AKI [12].

A continuous approach to renal replacement therapy (CRRT) for critically ill patients was introduced in 1977 and was hailed almost immediately as an improved alternative to intermittent hemodialysis (IHD). CRRT is the closest modality that can achieve and maintain a physiological hemodynamically unstable or severely catabolic patients with ARF.

The CRRTs represent a spectrum of treatment modalities. Access for CRRT may be via dual venous access (CVVH, CVVHF, CVVHDF) or via arterial and venous access (CAVH, CAVHF, CAVHDF). Initially, CRRT was provided using an arteriovenous extracorporeal circuit [13-18]. Although this approach offered technical simplicity, blood flow was dependent upon the gradient between mean arterial and central venous pressure and there was an increased risk of complications from prolonged arterial cannulation [19]. As a result, the continuous arteriovenous therapies have largely been supplanted by pump-driven, venovenous CRRT [20-22]. The modalities of venovenous

CRRT vary primarily in their mechanism of solute removal: in continuous venovenous hemofiltration (CVVH), solute transport occurs by convection; in continuous venovenous hemodialysis (CVVHD), it occurs by diffusion; and in continuous venovenous hemodiafiltration (CVVHDF), it occurs by a combination of the two [23-25]. Although, at the same level of urea clearance, convective therapies provide enhanced clearance of higher-molecular-weight solutes than diffusive therapies, no clear clinical benefit has been demonstrated for CVVH or CVVHDF compared with CVVHD. All continuous therapies use highly-permeable filters such that the bulk of solute removal occurs by convective transfer [11]. Convective solute removal is less efficient than diffusive, but the continuous nature of the therapy compensates for this and bulk solute removal has been reported to be higher than with IHD [26]. In some forms of CRRT dialysate is run countercurrent to the blood flow, so that the diffusive solute removal of hemodialysis is combined with the convective solute removal of hemofiltration. This form of RRT called hemodiafiltration (HDF) has been reported to offer superior solute removal. The clearance of urea and other small solutes during CRRT is proportional to the total effluent flow rate (the sum of ultra-filtrate and dialysate flow rates) [27] and dose of therapy is usually expressed as the effluent volume indexed to body weight.

CRRT offers extraordinary physiological and practical advantages over intermittent Hemodialysis or Peritoneal Dialysis in the treatment of Severe AKI. With CRRT, volume control is continuous and immediately adaptable to the rapidly changing clinical circumstances commonly seen in critically ill patients. Because of this adaptability, CRRT can immediately treat volume overload or prevent it without inducing acute volume depletion. The avoidance of intravascular volume depletion and hypotension is likely to prevent treatment-associated ischemic renal injury, which has been reported during standard Intermittent Hemodialysis [22].

CRRT is also indicated for patients at risk of or with increased intracranial pressure (neurosurgical patients, patients with encephalitis, meningo-encephalitis, or acute liver failure). CRRT prevents the surge in intracranial pressure associated with intermittent therapies.

The clinical benefits of HF have also been reported for cardiac surgery patients. The possible mechanisms include decreased fluid overload, myocardial edema, a decrease in left ventricular end diastolic pressure, optimization of the Starling relationship, increased myocardial performance, and the removal of circulating myocardial depressant factors.

Sepsis and the non-infectious systemic inflammatory response syndrome (SIRS) are a major cause of Acute Kidney Injury. CRRT appears to have beneficial effects on hemodynamics and inflammation in sepsis, thus providing a biologic rationale for using CRRT in septic shock and AKI in humans. Standard CRRT technology has been modified by either using a more permeable membrane, coupling continuous plasma filtration

with continuous adsorption or increasing the plasma water exchange rate [26]. These modifications are aimed at moving CRRT from the simple treatment of ARF to the adjunctive treatment of sepsis, but whether they can yield clinically significant benefits remains unknown.

While these advantages are widely reported, they are not universally accepted. A Cochrane meta-analysis in 2007 showed an advantage of CRRT over intermittent therapy in patients with AKI in variables that reflect hemodynamic instability (hypotension, mean arterial blood pressure and need for vasopressor drugs), but there was not enough evidence of ultimate improvement in survival. A large multicenter trial comparing intermittent hemodialysis with CVVH in ARF patients found no difference in 60 days survival. Since CVVH is costly, research to demonstrate a survival benefit is needed to support any routine use in MODS treatment. A number of authoritative reviews that have addressed the pros and cons of IHD versus CRRT for patients with ARF have been unable to provide objective evidence of the superiority of one approach over the other. Because, available recent data do not support the hypothesis that CRRT will provide better outcomes than IHD. In the only randomized, crossover study reported to date, the hemodynamic response to IHD and continuous hemofiltration were similar. The principal disadvantages of CRRT modalities include the need for prolonged systemic anticoagulation, with attendant risk of major bleeding, and the requirement for additional nursing and other resources. Clotting of the extracorporeal circuit occurs frequently with CRRT, which may increase blood loss and exacerbate anemia. Recently, several safety concerns have been raised with a CRRT delivery device. In some circumstances, CRRT is performed by personnel who are less experienced in the procedure than trained nurses who perform IHD. The use of CRRT, moreover, may enhance removal of amino acids, vitamins, small peptide hormones, catecholamines, and other solutes with beneficial function in critically ill patients.

The mortality for AKI patients who require renal replacement therapy in an ICU setting is estimated to be 50% to 70%, a figure that has changed little over the past 30 years, despite advances in medical care [4]. The failure to reduce AKI mortality may be due, at least in part, to increases in the age and complexity of current patients with AKI.

Of the factors that do appear to influence the mortality rate, the most important are:

- i. The primary diagnosis or underlying cause of the ARF.
- ii. The number of failing organ systems. In a prospective study carried out in South Wales hospitals, Sivalingam, et al. (2001) described cases deemed to require high dependency care who were instead managed on general wards. There was a significant association between inappropriate site of care and mortality.

Co-morbid factors which influence mortality rate are chronic heart failure, myocardial infarction, respiratory failure, sepsis,

and malignancy. The literature is conflicting with regard to the effect on AKI mortality of pneumonia, diabetes mellitus, and immune deficiencies.

AKI is a growing problem. Contributors to the growth of AKI include increases in the known precipitants of AKI such as sepsis, major surgery and congestive heart failure, higher age and co-morbidity burden of patients that increase the risk of AKI including CKD, proteinuria, diabetes, and obesity, and the broadening repertoire of medications that either are directly nephrotoxic or may lower the threshold for sustaining AKI. Reducing the burden of AKI will require identifying those experiencing the fastest growth in AKI and its complications, and research that identifies modifiable targets to prevent, treat and reduce the impact of this disease. Such studies will help in identifying the factors that may predict the outcome of AKI requiring RRT which would be useful in assessing current therapeutic approaches, research and resource allocation, and future therapies.

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