State of the Art: "Hemodialysis" Dose and Survival in Acute Kidney Injury

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INTRODUCTION

Acute kidney injury is increasingly being recognized as an independent correlate of poor outcomes, especially in hospitalized patients [1,2,3,4]. The incidence of AKI varies widely across different studies from different countries, in part due to different definitions and terminology [5]. There are very active efforts to establish both pharmacological and non-pharmacological therapeutic options for AKI. However, currently the only approved treatment for established AKI by the US Food and Drug Administration is dialysis [6]. A minimum standard dose of dialysis has been established for patients on maintenance dialysis for ESRD (End Stage Renal Disease). This paper is a review of such efforts to determine the minimum effective dose of "hemodialysis" that has a positive effect on mortality in AKI patients. Some of the studies reviewed used hemofiltration solely or in combination with hemodialysis as therapy.

Definition of Acute Kidney Injury

There have been various attempts to have a unanimous definition of acute kidney injury (AKI) [7,8]. Various clinicians and investigators have defined AKI as "an increase in creatinine >0.5mg/dl", others have termed it "an increase in serum creatinine concentration >50% or decline in creatinine clearance by 50%" while some definitions involves classifying AKI into stages based on severity [11]. Two major classification systems have been developed in an effort to standardize the definition of AKI.

The RIFLE criteria which classifies AKI into 5 stages; Risk, Injury, Failure, Loss, ESRD, [8] has been validated in various settings and has led to some clear standardization in the definition of AKI while the AKIN staging system is also similar to the RIFLE criteria and utilizes the same parameters, rise in serum creatinine and urine output to categorize AKI into three stages, AKIN 1, 2 and 3[7]. Although these systems may be validated, applying them in daily clinical practice is often cumbersome and many times impractical .

The RIFLE classification of AKI

There have been close to 35 different definitions used in the literature to define AKI [45] with no consensus on how AKI should be defined. This has led to difficulty with comparing studies and quantifying the incidence, prevalence and outcome associated with AKI. In 2004, the Acute Dialysis Quality Initiative convened an international interdisciplinary group that proposed the RIFLE criteria for definition of AKI[8]. Various studies have also validated the RIFLE criteria across diverse patient populations and hospital settings[4,46-49]. The RIFLE criteria consists of 5 stages with the first three stage representing stages of increasing severity (Risk, Injury and Failure) while the final two stages are outcome groups (loss and ESRD). It has been used increasingly in medical

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literature and is very useful in comparing or combining data across studies.

Hoste *et al* [2] reviewed studies using the RIFLE criteria to define AKI. The studies were easily comparable because they all used the same criteria to define AKI. They found that increasing RIFLE stage was associated with increasing mortality in most studies and that AKI patients treated with renal replacement therapy had a mortality rate as high as 50-60%.

The RIFLE Classification

	GFR/Creatinine criteria	Urine Output criteria
Risk	Increase in creatinine x1.5	UO < .5ml/kg/hr for 6hrs
	Or GFR decrease >25%	
Injury	Increase in creatinine x 2	UO < .5ml/kg/hr for 12hrs
	Or GFR decrease >50%	
Failure	Increase in creatinine x 3	UO < .3ml/kg/hr for 24 hrs
	Or GFR decrease >75%	or Anuria for 12hrs
Loss	Persistent ARF = complete loss of renal function > 4 weeks	
ESRD	End Stage Renal Disease > 3 months	

The AKIN classification of AKI

The Acute Kidney Injury Network (AKIN), an independent collaborative network of experts from various societies including Acute Dialysis Quality Initiative (ADQI) group, American Society of Nephrology (ASN), National Kidney Foundation (NKF), International Society of Nephrology (ISN) and the European Society of Intensive Care Medicine met in September 2005 in Amsterdam, Netherlands and proposed a definition and staging system for AKI known as the AKIN classification of AKI [7]. The AKIN group defined AKI as "an abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine of more than or equal to 0.3mg/dL, a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5ml/kg per hour for more than six hours)".

Lopes *et al* [9] conducted a retrospective study to analyze clinical characteristics of septic AKI using the AKIN classification and to assess its ability to predict in-hospital mortality of patients with sepsis. The study found the AKIN criteria as a simple and

The AKIN Classification

Stage	Serum creatinine criteria	Urine output criteria
1	Increase in creatinine e0.3mg/dL or increase eH150% to 200% from baseline	Less than 0.5ml/kg per hour for more than 6 hours
2	Increase in creatinine >200% to 300% (>2-to 3-fold) from baseline	Less than 0.5ml/kg per hour for more than 12 hours
3	Increase is creatinine >300% (3-fold) from baseline or serum creatinine of more than or equal to 4.0mg/dL with an acute increase of at least 0.5mg/dL for 24 hours or anuria	Less than 0.3ml/kg per hour for less than 12 hours

valuable tool in characterizing and stratifying septic patients according to the risk of death.

The fact that a clear definition is pivotal in identifying a condition and managing outcomes cannot be overemphasized. Contrast induced acute kidney injury on the other hand has been clearly defined as "a rise in creatinine greater than 0.5mg/dl or >25% rise in creatinine from baseline" [10] and this clear cut definition has led to earlier diagnosis of the condition and may lead to better outcomes.

The definition criteria used to define AKI could lead to significantly different incidence figures for AKI. Chertow *et al* [11] demonstrated that the criteria used to define AKI can lead to wide variation in the incidence of AKI and odds of mortality associated with AKI. The authors applied nine different but commonly used definitions to define AKI with a serum creatinine of e"0.3mg/dL being the most sensitive and a serum creatinine e"2.0mg/dL as the most specific definition. The prevalence of AKI depending on the definition varied from 1 to 44% and mortality associated with AKI ranging from an odds ratio of 4.1 to 16.4. In the study, when AKI was defined as rise in serum creatinine of e"0.5mg/dl, the incidence of AKI and odds ratio for mortality were 12% and 6.5 as opposed to 0.5% and 16.4 if the criteria was e" 2.0. This shows the wide variation in incidence data and outcomes associated with the lack of a universally accepted and practiced definition of AKI.

Epidemiology of Acute Kidney Injury

The prevalence and hospital mortality associated with AKI in various regions of the world vary significantly [5]. Single center studies [12-18] have given estimates between 1% and 25% while multicenter studies [19-26] gave estimates as high as 39 - 71%. The use of different criteria for AKI definition may explain the wide variation in prevalence estimates. Most studies on AKI prevalence and outcome were conducted in Europe, North America and Australia.

Considering the paucity of data on the epidemiology and outcome of AKI in other regions of the world, Uchino et al [5] conducted a large multi-center study in 23 countries to determine the prevalence of AKI in the ICU and determine factors which impact patient outcomes. The criteria for AKI in the study were oliguria of less than 200 mL in 12 hours and/or marked azotemia defined as defined as a blood urea nitrogen level higher than 84mg/dL. This definition unfortunately does not readily correlate with the AKIN classification of AKI, the RIFLE criteria or percentage/quantitative rise in creatinine as often used in clinical practice. Countries included in this study were mainly in Europe and North America, although centers in Asian and South American nations were also included. A total of 1738 of the 29,269 critically ill patients included in this study developed AKI requiring renal replacement therapy (RRT) during their hospital stay. This places the prevalence of AKI at 5.7% although there was considerable variation in the figure from country to country (United Kingdom: 20.6% and Israel: 2.1%). The overall hospital mortality was 60.3% with septic shock as the most common contributing factor to AKI (47.5%), major surgery (34.3%), cardiogenic shock (26.9%) and hypovolemia (25.6%).

Anochie *et al* [27] studied the prevalence, etiology, management and outcomes of AKI in children in Southeastern Nigeria. A total of 211 patients were enrolled with ages between 5 days and 16 years. Oliguria was the most common clinical feature (87.2%). The hospital prevalence was estimated at 11.7 cases/year. Birth asphyxia accounted for 35.5% of the AKI cases, Septicaemia (22.4%), gastroenteritis (28.9%), malaria (13.7%), congenital malformations (14.5%) and tetanus (5.3%). There was an indication for dialysis in 108 patients but only 24 patients received renal replacement therapy in the form of peritoneal dialysis due to lack of financial resources and dialysis equipment. Mortality rate was as high as 40.5%. Hypertension, lack of dialysis, delayed presentation, herbal medication use and lack of finances significantly affected outcomes negatively. Olowu and Adelusola [28] prospectively studied the prevalence, etiology and outcomes of AKI in children in Southwestern Nigeria. A total of 123 patients were studied while only 10 had dialysis (Peritoneal dialysis: 7 and hemodialysis: 3). Patients were enrolled over a 9 year period with a mean age of 6.28 years. The overall mortality associated with AKI was also as high as 46.2% which is similar to the study in southeastern Nigeria with factors such as financial limitations, inadequate or lack of dialysis equipment and late presentation as significant factors in such high mortality figures.

Mortality in Acute Kidney Injury

AKI has been suggested to be an independent risk factor for mortality [1]. Often times, AKI exists in a background of life threatening illnesses and this also contributes or may be responsible for the high mortality associated with AKI [1]. Co-morbid

conditions that are associated with AKI may also necessitate procedures such as radiocontrast exposure and surgery leading to blood loss and hypotension thus increasing the risk of renal injury. The exact contribution to mortlaity played by AKI or the underlying conditions is not very clear.

Levy *et al* [1] conducted a large study to test the hypothesis that underlying conditions account for the high mortality rate in AKI. The study involved 16248 inpatients who underwent radiocontrast studies between 1987 and 1989. The mortality rate in patients with AKI was 34% compared to 7% in patients without AKI with the odds ratio of death in patients with AKI being 5.5 after adjusting for differences in comorbidity. This study goes to prove that AKI is an independent risk factor for mortality and that the underlying conditions alone cannot explain the high mortality rate associated with AKI.

The mortality rate associated with AKI is dependent on the severity of the underlying conditions, if any, and the location in the hospital. For instance, AKI in the absence of any other co-morbid condition is associated with a mortality of 7 to 23% while in the ICU; the mortality is as high as 50 to 80%. Also survival after AKI is largely dependent on number of failed organs with mortality less than 40% if there is no organ failure as opposed to a mortality rate of greater than 80% if 3 or more organs have failed.

Acute Kidney Injury and Dialysis

Acute Kidney Injury is a condition with very diverse etiology, a spectrum of disease staging and occurs through different pathophysiologic pathways. Many agents have been used to treat AKI with limited success. Some agents may be more efficacious if started before the injury. Diuretics, low dose dopamine, mannitol, theophylline, prostaglandins, natriuretic peptides, saline and N-acetlylcysteine are part of the long list of agents that have been used to treat AKI with limited success [29]. However, as it stands, the only United States Food and Drug Administration approved treatment for Acute Kidney Injury (AKI) is dialysis [6]. The indication for dialytic intervention in the ICU/critical care patients include but are not limited to hyperkalemia, academia, uremia, volume overload, toxin removal, and as support modality for fluid management in multi-organ failure. There has been so much debate on the frequency, dose, modality and timing of dialysis initiation that will yield the best patient outcomes. Unfortunately, there is often no single answer to these issues because unstable patients in the critical care setting often have varied concomitant conditions (e.g. sepsis, acute lung injury) that could influence the dialysis prescription. Significance of increased fluid intake in the form of medication, blood products, total parenteral nutrition as well as high catabolic rate in these unstable patients have to be considered in deciding the choice of dialysis modality, dose, frequency and time of initiation. Intermittent hemodialysis is often poorly tolerated in unstable patients in the critical care setting with continuous venovenous hemodialysis associated with less hemodynamic instability and possibly improved survival via more efficient removal of immunomodulatory substances. Although there are a few studies out there that try to answer questions such as; what is the optimal dose for hemodialysis? When should hemodialysis be initiated? Is daily intermittent hemodialysis superior to alternate day hemodialysis? Is a continuous regimen hemodialysis associated with better outcomes when compared to intermittent daily hemodialysis, there is still a lack of consensus on the optimal treatment of critically ill patients with acute kidney injury.

Venkataraman *et al* [30] retrospectively studied the dosing patterns of continuous renal replacement therapy (CRRT) in patients with AKI and discovered that the dose of CRRT delivered in most patients is lower than the prescribed dose. Clotting of the system played a major role in the lower delivered dose while hemodynamic instability was not a factor.

The optimal time to initiate dialysis is still debatable. Aggressive and early initiation could be associated with prolonged duration of AKI, decreased urine output, complement activation and hypotension. On the other hand delaying dialysis may be associated with complications such as volume overload from bicarbonate infusion or poor nutrition due to fluid restriction.

Many large studies have been conducted to give answers to the optimal dose, frequency and time of initiation of dialysis for better patient outcomes. Gillium *et al* study [31] is one of the earlier studies on the role of intensive dialysis in acute renal failure. This was a prospective study carried out on 34 patients whom were paired by acute renal failure etiology and treated with sufficient dialysis with the goal of maintaining predialysis blood urea nitrogen and serum creatinine below either 60 mg/dl and 5mg/dl (intensive treatment group) or 100mg/dl and 9mg/dl, respectively (less intensive group). The results of the study that the overall complication rates were not different

between the two groups. The mortality rates were not significantly different between the two groups; 58.8% in the intensive group and 47.1% in the non-intensively dialysed group. This study thus preceded other larger studies on dialysis dose and survival.

Ronco *et al* [32] undertook a randomized prospective study of the impact different ultrafiltration (UF) doses in continuous renal replacement therapy on patient survival. 425 patients with AKI admitted to two different intensive-care units of the same institution were enrolled in the study. Patients were enrolled over a five year period and the mean age of the study population was 61 years. The patients were randomly assigned to receive an ultrafiltration treatment at one of three doses: 20mL/kg/h (group 1); 35mL/kg/h (group 2); or 45mL/kg/h (group 3). The primary endpoint was survival at 15 days after stopping ultrafiltration. Rate of recovery of renal function and frequency of complications during treatment were also assessed. The results showed that survival in the group which received a UF dose of 20mL/kg/h was significantly lower than that of groups 2 (P=0.0007) and 3 (P=0013). However, survival in the groups that received a UF dose of 35mL/kg/h did not differ from those that received a dose of 45mL/kg/h (P=0.87). There was no change in the pattern of differences amongst groups after adjustments for possible confounders were made. Full recovery of renal function was as high as 95%, 92% and 90% in groups 1, 2 and 3 respectively while frequencies of complications were similar and low across all three groups. This study thus suggests that increasing the dose of ultrafiltration for critically ill patients with AKI improves survival significantly. Hence, they recommended a minimal ultrafiltration dose of 35mL/kg/h for critically ill patients with AKI. Saudan *et al* [33] also studied the effect of dialysis dose on survival. It was a three year prospective randomized trial with the hypothesis that an increase in dialysis dose achieved by continuous veno-venous hemodiafiltration (CVVHDF) is associated with a better survival when compared to continuous veno-venous hemofiltration (CVVH). 206 patients critically ill patients with AKI were randomized into 2 groups: CVVH (1-2.5l/h replacement fluid) or CVVHDF (1-2.5l/h replacement fluid + 1-1.5l/h dialysate). Outcome measures assessed were 28 and 90 day mortalities, renal recovery and duration of ICU stay. The 28-day (P=0.03) and 90-day (P=0.0005) survivals were significantly better in the CVVHDF group compared to the CVVH group. The result supports the Ronco study and suggests that increasing the dialysis dose in severely ill patients with AKI, improves survival.

Tolwani *et al* [34] studied the effect of dosage of continuous venovenous hemodiafiltration (CVVHDF) on survival in patients with acute renal failure. 200 critically ill patients with AKI were randomly assigned to receive CVVHDF at either a high dose of 35ml/kg/hr or a standard dose of 20ml/kg/hr. The primary outcome was survival to the earlier of either intensive care unit discharge or 30 days. Outcome rate in the high dosage group was 49% while that in the standard dosage group was 56% (P=0.32). Renal function recovery amongst hospital survivors was also similar. 69% of those in the high dosage group and 80% of those in the standard dosage group recovered renal function (P=0.29). The results thus did not show a difference in patient survival or renal recovery between patients receiving high dose CVVHDF or standard dose CVVHDF.

Schiffl *et al* [35] studied the role dialysis frequency had to play in the survival of patients with AKI. It was a prospective study comparing the effect of daily intermittent hemodialysis as opposed to intermittent (alternate day) on survival among patients with AKI. A total of 160 patients with AKI in the medical and surgical intensive care units were assigned in alternating order to receive either daily or intermittent hemodialysis for AKI over a 5 year period. The primary endpoint of the study was survival while duration of AKI and the frequency of therapy-related complications were secondary endpoints. The baseline characteristics including APACHE (Acute Physiology, Age and Chronic Health Evaluation) III scores between the two groups were similar. There was better control of uremia, fewer episodes of hypotension during hemodialysis and more rapid resolution of AKI in the daily hemodialysis group as opposed to the intermittent hemodialysis group (P=0.001). The mortality rate was also significantly different between the 2 groups; 28% in the daily hemodialysis cohort and 46% in the intermittent hemodialysis cohort (P=0.01). This study supports the hypothesis that more intensive hemodialysis through more frequent sessions is associated with reduction in mortality in critically ill patients with AKI and is not associated with increased incidence of hemodynamically induced morbidity. This study thus supports the argument that more hemodialysis is better especially in patients with AKI. The limitation of practicing daily hemodialysis is that it has huge

financial and staffing implications. Also, the mortality in the intermittent hemodialysis cohort was 46%, a rate that is lower than most studies on AKI in severely ill patients in ICU's. The lower rate may be explained by the fact that the patients in Schiffl et al's study were less severely ill and most patients were not oliguric at the time of enrollment. Nevertheless, daily hemodialysis may be superior to alternate-day hemodialysis because it is associated with less dramatic variation in plasma concentrations of solutes and cytokines, a reduced requirement for fluid removal and thus less hemodynamic instability. Less severe instability may be associated with lower incidence of ischemia.

Gettings *et al* [36] assessed the role of timing of initiation of continuous renal replacement therapy (CRRT) had to play on outcomes in patients with post-traumatic AKI. It was a retrospective study that characterized the patients as either early or late starters based upon whether the blood urea nitrogen was less than or greater than 60mg/dL prior to CRRT initiation. CRRT was thus initiated earlier in early starters as compared to late starters. The 2 study groups were however similar with respect to Injury Severity Score, admission Glasgow Coma Score, presence of shock at admission, age, gender distribution and trauma type. The results showed that survival rate was significantly higher in early starters as compared to late starters (39.0 vs 20.0%, P=0.041) suggesting that an earlier initiation of CRRT in patients with AKI may improve survival.

Bouman *et al* [37] studied both the role of time of initiation of continuous venovenous hemofiltration and the dose (ultrafiltration rate) of hemofiltration on mortality and renal function recovery. It was a randomized, controlled two-center study on 106 ventilated severely ill patients with AKI. The patients were randomized to either of 3 groups; early initiation of high-volume hemofiltration (72-96L/24hrs), early initiation of low volume hemofiltration (24-36L/24hrs), and late low-volume hemofiltration (24-36L/24hrs). Survival at 28 days (P=0.80) and median duration of renal failure (P=0.25) were similar amongst all three groups. The study thus concludes that in severely ill patients with oliguric AKI, survival at 28 days and recovery of renal function were not improved by the use of higher hemofiltration dosage or earlier initiation of hemofiltration.

The Veterans Affairs/National Institutes of Health (VA/NIH) Acute Renal Failure Trial Network Study [38] is a multicenter, prospective, randomized trial of the intensity of renal replacement therapy in critically ill patients with AKI conducted in 27 VA and university-affiliated medical centers in the United States. 1124 critically ill patients with AKI were randomly assigned to receive either an intensive or less intensive renal replacement therapy. In both strategies, hemodynamically stable patients received intermittent hemodialysis while unstable patients underwent continuous veno-venous hemodiafiltration (CVVHDF) or sustained low-efficiency dialysis (SLED). The intensive treatment strategy entailed intermittent hemodialysis and SLED six times a week and CVVHDF at 35mL/kg/h while the less intensive treatment strategy intermittent hemodialysis and SLED three times a week and CVVHDF at a lower dose of 20mL/kg/hr. The primary endpoint of the study was death from any cause by day 60. The results showed that there was no significant difference between the two groups with respect to the death from any cause by day 60 (OR: 1.09, P=0.47), duration of renal replacement therapy, rate of recovery of kidney function or nonrenal organ failure. Hence this large, recent and landmark study refuted all earlier studies and suggests that intensive strategy of renal replacement therapy in severely ill patients with AKI does not decrease mortality as compared to a less intensive strategy.

The unique feature of the VA/NIH study as compared to other studies is that it allowed patients to move from one mode of renal replacement therapy to another as long as they stayed within the originally assigned intensive or less intensive treatment group. Although the VA/NIH did not show the benefit of increasing intermittent dialysis treatments to five to six times per week, it however did not disprove the fact that dose does matter. Since the targeted standard dialysis dose in the study was greater than what is often achieved in intermittent hemodialysis, increasing the dose further did not show any significant difference in outcomes. Hence, the VA/NIH study suggests that increasing the frequency of intermittent hemodialysis more than three times per week, in hemodynamically stable patients, with a target achieved Kt/V_{urea} of 1.2 to 1.4 per treatment or provision of continuous renal replacement therapy to hemodynamically unstable patients at a dose higher than 20ml/kg/hr was not associated with improved outcomes.

While there has been so much debate on the optimal dose of dialysis in patients with AKI, there has been a lot of variation in the practice from country to country and even amongst ICU's in the same

country. Uchino and colleagues [39] studied the practice of continuous renal replacement therapy (CRRT) for treatment of AKI and possible clinical effect of practice variation amongst 54 ICU's in 23 countries. The results showed that the (CRRT) practice varied significantly across the units did not follow best evidence.

Kellum's meta-analysis [40] of four major studies [32, 33, 35, 37] which addressed dosing of hemodialysis and survival outcome showed a significant survival advantage in favor of a higher dosing (OR:1.95, P<0.001). The pooled studies were homogenous (Q statistic 1.73, P=0.63).

CONCLUSION

There have also been extended alternatives to continuous renal replacement therapy. Pulse high-volume hemofiltration as an adjuvant treatment of severe sepsis is a new modality which aims at much higher doses of hemofiltration at rates up to 120ml/kg over short periods (6-8hours/day) and is associated with improved hemodynamics pre- and post-treatment and may have patient survival benefits [41].

Extended daily dialysis refers to the use of conventional hemodialysis daily at slow flow rates over an extended treatment time. In comparison to continuous venovenous hemofiltration, extended daily dialysis has the advantage of requiring less anticoagulation and less nursing care, easier to perform and offers the same benefits provided by continuous venovenous hemofiltration such as hemodynamic stability and volume control[42,43]. Sustained low-efficiency dialysis is also another dialysis treatment strategy in critically ill patients and involves use of the conventional hemodialysis setup to achieve hemodialysis at reduced dialysate and blood flow rates [44].

As we await the publication of the RENAL (Randomized Evaluation of Normal vs. Augmented Level of renal replacement therapy in ICU) study results which is the largest ever continuous renal replacement therapy trial completed there is still a lack of agreement on the optimal dose of dialysis for critically ill patients with AKI.

The best evidence that exists supports the use of at least 35ml/kg/hr dialysis dose for CVVH (Continuous Venovenous Hemofiltration), CVVHDF (Continuous Venovenous Hemodiafiltration) or daily hemodialysis.

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