Review Article

Renal Replacement in the Critically ill with Acute Kidney Injury: When and How to Initiate Therapy

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Abstract:

Although Acute Kidney Injury (AKI) is a common complication in the critically ill, there is still no specific therapy. Similarly the diagnosis of AKI, while regulated by specific criteria, is not free from pitfalls. Newer biomarkers are also being added in the diagnostic panel that helps in identifying the stage, severity and underlying cause of this condition. When preventive and supportive management fails, Renal Replacement Therapy (RRT) becomes necessary. RRT is one of the most invasive management procedures and it is associated with many complications. Hence the time of onset and the modality of choice are two of the most puzzling aspects of this procedure. Over the last decade and a half, a lot of RCTs, observational studies and meta analyses have been carried to find the exact answer to these questions. While all the answers are not yet simplified, we have specific guiding parameters now as to the choice of modality and onset of dialysis for AKI. There is still need for further research for more specific answers to these age old questions.

Key words: Acute Kidney Injury, Critically ill patients, Intensive Care Unit, Renal replacement therapy.

Introduction:

Acute Kidney Injury (AKI) is very common among patients in Intensive Care Unit (ICU); as much as 50% of critically ill patients suffer from it[1]. Although the treatment of AKI is mostly supportive with renal protective measures and through renal replacement therapy (RRT), much argument persists regarding the time of initiation of RRT as it poses much risk to the patient due to the invasive nature and the preexisting co-morbidities of the critically ill.

Moreover there is significant difference in outcome of sepsis with AKI and without AKI. It is now proven that AKI is not only an epiphenomenon of severity but an independent mortality factor in sepsis patient[2].This review will try to shade light on the updated definition of AKI, its brief epidemiology and risk factors among the critically ill and finally on the time of onset of RRT along with the modalities used.

Definition of AKI:

The first systematic definition of AKI was presented in 2004 through the Risk, Injury, Failure, Loss, End-stage (RIFLE) criteria. Here, for the first time a urinary output of less than 0.5ml/kg/hr for more than 6 hours was included along with a rise in serum creatinine by 1.5 fold from baseline. This definition further evolved with the 2007 AKI Network (AKIN) classification and in 2012 both the RIFLE and AKIN definition were merged in the Kidney Disease Improving Global Outcomes (KDIGO) classification. It is to be noted that since 2012 this definition has not been modified and is now widely accepted in the clinical setting.

Diagnostic Criteria of AKI according to KDIGO[3]:

AKI is defined as increase in serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 µmol/l) within 48 hours;

or increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; **or** urine volume <0.5 ml/kg/h for 6 hours. Table I shows KDIGO staging of AKI.

Table I: KDIGO staging of AKI

AKI stage	Serum creatinine criteria	Urine output criteria
AKI stage I	Increase of serum creatinine by ≥ 0.3 mg/dl (≥ 26.4 µmol/L) or increase to 1.5 – 1.9 times from baseline	urine output <0.5 ml/kg/hr for 6-12 hrs
AKI stage II	Increase of serum creatinine to 2.0 – 2.9 times from baseline	urine output <0.5 ml/kg/hr for ≥ 12 hrs
AKI stage III	Increase of serum creatinine ≥ 3.0 times from baseline or serum creatinine ≥ 4.0 mg/dl (≥ 354 µmol/L) or treatment with RRT or in patients <18 yrs, decrease in estimated GFR to <35 mL/min per 1.73 m^2	urine output <0.3 ml/kg/hr for ≥ 24 hrs or anuria for ≥ 12 hrs

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Recovery and Duration:

The 16th Acute Dialysis Quality Initiative Consensus document of 2017 defined the recovery and duration of AKI in accordance with the KDIGO definition[4]. Significant aspects of this definition are as follows:

a) Persistent acute kidney injury (AKI) is characterized by the continuance of AKI by serum creatinine or urine output criteria (as defined by KDIGO) beyond 48h from AKI onset.

b) Complete reversal of AKI by KDIGO criteria within 48h of AKI onset characterizes rapid reversal of AKI.

c) AKI and acute kidney disease (AKD) are a continuum, and persistent AKI frequently becomes AKD, defined as a condition wherein criteria for AKI stage 1 or greater persists ≥7 days after an exposure.

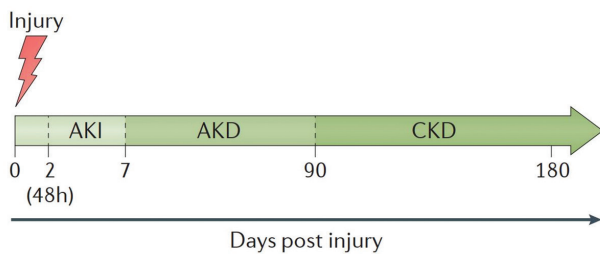d) If AKD is present on day 90, it becomes chronic kidney disease.

Fig: 1: Continuum from AKI to AKD and to CKD in days. (Modified from Acute Dialysis Quality Initiative 16; www.adqi.org.)

Sepsis associated AKI (S-AKI):

In 2016, sepsis was redefined as "life threatening organ dysfunction caused by a dysregulated host immune response to infection." It was noted early on that kidney was one of the organs that was hit in the earliest phases of sepsis and it develops in more than two-third patients with septic shock[5]. Hence Sepsis associated AKI (S-AKI) is a term often coined but lacks any consensus definition. But based on current understanding it may be defined as a clinical syndrome characterized by abrupt deterioration of renal function (as quantified according to the KDIGO criteria) in the presence of sepsis without other meaningful explaining factors[6].

The difficulty in diagnosis of AKI in the critically ill:

As evident from the above discussion, serum creatinine remains the cornerstone of diagnosis of AKI. But there are some pitfalls in its use despite the development of modern scientific measurement techniques. Furthermore, diagnosis of AKI in the critically ill is further complicated by the pathophysiology of sepsis itself.

Creatinine is the metabolic end product of creatine phosphate which in synthesized from glycine and arginine, mainly in the liver and kidneys. In health, its production is dependent on muscle mass, meat intake and the amount of creatine phosphate generated in liver and kidney but during critical illness it is noted that the production of creatinine may

decreased significantly for a sustainable period of time[7].

There are several pitfalls in using creatinine in the diagnosis of AKI[8-10].

e) Serum concentration may take 24-36 hours to rise.

f) There is lack of standardized laboratory methods for quantifying serum creatinine and some substances both internal and external (like billirubin, 5-flucytosine) may interfere with determination.

g) Heavily affected by volume status as it is measured as a concentration. As a result diagnosis may be delayed in patients with volume overload.

h) Creatinine-based definition of AKI requires a reference 'baseline' value which is not always available. Surrogate estimates like estimated glomerular filtration rate (eGFR) is commonly used which may both increase or decrease the true incidence.

i) It does not take into account the underlying renal reserve. This becomes a big issue in patients not diagnosed previously as having CKD.

j) Not reliable in patients with sepsis, liver disease and/or muscle wasting.

The problem of diagnosing AKI in sepsis needs to be implored further. The standard ways of measuring glomerular filtration rate (GFR) is with inulin, ^{51}Cr-EDTA or inohexol. But these processes are very time consuming and complicated, hence not suitable for ICU patients. There are several equations like the modification of diet in renal disease (MDRD) or chronic kidney disease epidemiology collaboration (CKD-EPI), that are used for calculation of the eGFR. But these equations need serum creatinine to be a steady state, rather than the ever labile state it is usually found in septic patients. To find a solution to this problem, urinary creatinine clearance (CCr) has been used to estimate GFR[11].

Similarly, another point of reference used for diagnosing AKI, i.e. urinary output if not full proof either. There are significant physiological conditions where decreased output does not necessarily herald the onset of AKI, the most obvious being significant hypovolemia due to any cause. Similarly prolonged fasting, severe stress, post surgical stress, pain and trauma may all cause oliguria. The mechanism that is involved is increased secretion of the Anti-Diuretic Hormone (ADH) that causes concentration urine as a physiological response[12].

The arbitrarily fixed threshold of 6 hours of oliguria and also the body weight based limit of 0.5ml/kg/hr have also been challenged in several observations. Moreover in obese and morbidly obese patient this issue of urine output according to body weight becomes more problematic, so much so that the European Renal Best Practice Guidelines (2012) recommend using the ideal weight to avoid over diagnosis of AKI[13].

Cystatin C is another biomarker that has received significant attention over the last decade as an early diagnostic tool and marker of tubular injury. It is produced by all nucleated cell and its low molecular weight means it is readily filtered in

urine. With a healthy kidney, almost all of it is either reabsorbed or catabolized in the proximal tubules. Hence its presence in urine is a marker of tubular injury. On the other hand, its production of less affected by body mass and gender. It has a shorter half life; hence its serum level indicates earlier diagnosis of AKI, especially in critically ill patients[14]. This dual use of Cystatin C makes it an important biomarker to consider and further larger studies are required determine its actual application.

Newer biomarkers for AKI and for diagnosing renal recovery:

It is to be noted that serum Creatinine and Cystatin C level primarily reflects on glomerular filtration. Newer biomarkers have a wider range and can detect tubular stress, tubular damage and inflammatory changes. These markers are sensitive and their change is very dynamic making their use in diagnostic very time-sensitive. Some of these markers are

a) Tissue Inhibitor of Metalloproteinases 2 (TIMP-2)

b) Insuling like growth factor binding protein-7 (IGFBP-7)

c) Neutrophil Gelatinase associated Lipocalin (NAGL)

d) Kidney injury molecule-1 (KIM-1)

e) N-acetyl-β-D-glucosaminidase (NAG)

f) Liver fatty acid-binding protein (L-FABP)

g) IL-18

h) Chemokine ligand-14 (CCL-14)

While these biomarkers illuminate a new frontier of identifying AKI and its etiology, wider validation is not yet acquired. Serum creatinine still is the gold standard of diagnosis as per the guidelines and hence these biomarkers are used as supplementary investigations for identifying the underlying mechanism of AKI[14,15].

Indications of Dialysis[16]:

The indications of renal replacement therapy (RRT) in AKI can be broadly divided under two headings; absolute and relative. While the absolute indications warrant immediate start of dialysis without delay, for the relative indications, the clinician plays a fundamental part in the decision regarding the onset of dialysis.

Absolute Indications:

1. Refractory hyperkalaemia: Refractory severe hyperkalaemia can be defined as hyperkalaemia that does not respond to medical managements like bicarbonate, glucose-insulin infusion or beta-2 agonists. It is a medical emergency and if left untreated can give rise to cardiac conduction abnormalities and life threatening arrhythmias and muscle weakness. Although a specific threshold for dialysis cannot be defined, arbitrarily a range of >6 mmol/L is used as below this level, hyperkalaemia is usually safely managed by medical interventions. Special scenarios where there is ongoing potassium absorption from significant gastro-intestinal bleeding and muscle breakdown, this threshold can be lower.

2. Severe pulmonary oedema or diuretic resistant volume overload: In AKI patients, specially with anuria or oliguria, fluid overload is a very common phenomenon. In most cases the sign symptoms of volume overload are first approached by administration of adequate dose of intravenous loop diuretics and in some cases volume restriction. But with insufficient improvement in urine output and severe deterioration of respiratory function with hypoxemia, dialysis becomes inevitable.

3. Poisoning: Poisoning by a dialysable agent may require urgent initiation. The decision varies from patient to patient and with severity of symptoms. Some agents that require extracorporeal remover by dialysis are metformin, lithium, methanol and ethylene glycol.

Relative Indications[17]:

1. Metabolic acidosis: Metabolic acidosis is a very common finding in critically ill patients, even more so with patients with AKI as they are unable to preserve bicarbonate via kidneys. The first approach to metabolic acidosis is via medical management (like addition of bicarbonate) or ventilator manipulation and treatment of the underlying cause, but if these measures fail then a persistent metabolic acidosis with pH <7.15 requires dialysis.

2. Uraemia: Uremia defines a syndromic presentation of sign symptoms that is attributable to high urea levels in blood. It is common in AKI patients. These sign symptoms range from anorexia, nausea to alteration of mental status, asterixis and pericardial rub in association with development of uremic pericarditis. But presence of these features does not mean dialysis is always required. Patient with life threatening features of uremia like seizures or significant pericardial effusion may require dialysis. So daily monitoring of uremic feature is a key point in the decision making process.

When to start RRT:

The time to start renal replacement therapy is a question that plagues Critical Care Specialists and Nephrologists similarly. Critically ill patients have a plethora of problems like multiorgan failure, multiple co-morbidities of varying severity and they often have coagulation abnormalities, require aggressive fluid resuscitation and requires numerous medications, many of them nephrotoxic. These factors greatly compound the problem of the timing of initiation of dialysis[18].

Renal replacement therapy (RRT), in all its modalities, is one of the most invasive procedures used in the ICU with significant risks involved. Catheter related blood stream infection, haemodynamic instability (development of hypotension during dialysis, development of arrhythmias and so on) and metabolic abnormalities (dialysis disequilibrium syndrome and hypophosphataemia) are some of the major concerns. So it is understandable that starting dialysis before the absolute or relative indications are there is not advised.

Not to forget, that RRT is costly and labor intensive, especially in resource poor settings like the ICUs of Bangladesh. Hence a lot of studies have tried to answer this age-old question of when to start dialysis. Observational studies were not the correct tool to find this answer as these studies did not take into account those patient who did not receive dialysis despite having severe AKI. A randomized control trial (RCT) that compares both early and delayed dialysis initiation strategies was found to be the appropriate study design. Similarly, meta-analysis that looked into older and smaller trials were also a plausible source.

Two large multi-center RCTs, (the AKIKI trial[19] and the IDEAL-ICU trial[20]) were carried out to compare the earlier and delayed approach of RRT. The inclusion criteria in both trials included critically ill patients with severe AKI (RIFLE-F for IDEAL-ICU and KDIGO-3 for AKIKI). The patients were subjected to either an immediate or delayed RRT strategy after randomization. Both RCTs show no statistically significant variation of mortality between the two groups. Both RCTs showed that the delayed strategy allowed more RRT-free days in the surviving patients (17 vs 19, $p<0.001$ and 12 vs 16, $p=0.006$ in AKIKI and IDEAL-ICU, respectively). The AKIKI trial also highlighted that renal functional recovery was faster in the patients of the delayed strategy group.

In the Standard versus Accelerated Initiation of Renal-Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial, 3019 patients were included who were critically ill and had severe AKI but did not have an indication for RRT yet. These patients were randomly assigned to either early strategy (initiation of RRT within 12 hr of identification) or delayed strategy (RRT after any indication develops)[21]. The indications that were used in the delayed strategy group were pH <7.20, bicarbonate <12mmol/L, potassium >6mmol/L, type I respiratory failure due to pulmonary oedema or if the AKI persisted 72 hours after enrollment in the study.

In the early strategy group, 97% patient was started on RRT in comparison to 62% in the delayed strategy group. But no difference in mortality at 90 days were noted among the two groups (43.9% vs. 43.7%, p = not significant); however those assigned in the early strategy group were more likely to remain RRT dependent at day 90 (10.4% vs. 6.0%, p<0.05) and required more rehospitalizations (21% vs 17%). Based on the interpretation of these trials, clinicians now tend to prefer a delayed strategy when considering RRT.

In a meta-analysis of nine studies and 1879 patients[22], early RRT initiation did not decrease mortality at 28 (43 versus 44 percent), 60 (51 percent in both groups), or 90 days (56 versus 55 percent). While only 58% patient received RRT in the delayed group, it was 100% for the early intervention groups. There was no difference in adverse events like severe bleeding, life-threatening arrhythmias or development of hyperkalaemia. Neither was there any difference between the groups regarding RRT dependence during hospital discharge. The trials considered in the meta-analysis were of high quality and homogenous.

But the question of how much delaying in initiating dialysis is safe remains unclear. Here comes the Artificial Kidney Initiation for AKI 2 (AKIKI-2) trial[23] where 278 critically ill patients with severe AKI included. These patients did not have any urgent indications for dialysis at the time of enrollment. The delayed strategy group of patients was monitored for development of either oliguria of 72 hours duration or an elevation in BUN to between 112 and 140 mg/dL. The very-delayed group was started on RRT only if these criteria developed: Serum potassium >6mmol/L, BUN >140mg/dL, type 1 respiratory failure due to volume overload or persistent metabolic acidosis.

The primary outcome of this trial was RRT-free days at day 28 and neither of the group show any significant advantage over the other (12 days vs. 10 days, p=0.92). The mortality at day-28 and day-90 also did not vary between the study groups. It was also notable that only 21% in the very-delayed strategy did not receive RRT and regained renal function spontaneously. Furthermore in a multivariate analysis of variables associated with day-60 mortality, the very-delayed strategy was significantly and independently associated with increased mortality, along with higher SAPS-III scores and mechanical ventilation. Considering these findings together, it can be deducted that prolonged deferral of RRT in critically ill patients may be deleterious.

So to draw an inference, considering all the data across multiple RCTs, it can be said that early initiation of RRT in absence of any indication is deleterious for the patients and also misuses significant health resources. It also associated with delayed recovery of kidney function. But, there is a threshold, albeit poorly defined, beyond which delaying RRT may be harmful. This threshold varies from patient to patient and the decision relies heavily on the clinical and biochemical parameters.

Modalities of dialysis:

Dialysis depends on two basic principles. These are

1. Diffusion: Movement of molecules from a region of higher concentration to a region of lower concentration.

2. Convection: It is defined as a process of movement of solute with its solvent through a semi-permeable membrane.

All the modalities of dialysis use these two basic principles either in combination or separately.

Hemodialysis: This is based on the principles of diffusion. During hemodialysis blood is purified by passing it through a hollow fibred filter. This filter, in turn, is immersed in a sterile dialysate solution with an electrolyte composition close to plasma. Bi-directional solute exchanges occur across the membrane depending on:

- molecular size
- concentration gradients
- membrane permeability
- exchange duration
- relative blood and dialysate flows

Hemofiltration: This is based on the principles of convection where the pressure gradient between both sides of the dialysis filter drives the exchange of molecules irrespective of the concentration gradient. During hemofiltration a negative pressure is generated by the effluent pump and this pressure gradient leads to fluid movement through the membrane. As a result the size of water soluble molecules in relation to the pore diameter of the dialysis filter plays a central role here. Other factors are distribution volume, protein binding and electrical charge. A sterile substitution solute is added either before or after the filter to compensate for the loss of volume.

Hemodiafiltration: It used the combination of diffusion and convection principles. Hemodiafiltration is typically applied in the form of continuous veno-venous hemodiafiltration (CVVHDF).

The duration and frequency of giving dialysis varies depending on the patient's clinical condition. Here, again, RRT can be broadly divided into two types.

1. Intermittent haemodialysis (IHD): This is the standard and most commonly used modality of dialysis, especially in patients with end stage renal disease. But it is also often used in critically ill patients suffering from AKI. The dominant method here is diffusion and some haemofiltration, more commonly called ultrafiltration, for removal of fluid. It is usually given in sessions lasting 3-6 hours, daily or every other day.

2. Continuous dialysis: The continuous modalities, known as continuous renal replacement therapy (CRRT). It is usually given 24 hours a day and this offers slow and continuous removal of solute and fluid removal, preventing sudden changes in electrolyte and serum osmolarity. CRRT can be given in one of three following ways:

   - Hemofiltration (continuous veno-venous hemofiltration, CVVH)
   - Hemodialysis (continuous veno-venous hemodialysis, CVVHD)
   - Combination of both (continuous veno-venous hemodiafiltration, CVVHDF).

3. Hybrid strategies: Prolonged intermittent renal replacement therapy (PIRRT) is a combination of both intermittent and continuous modalities. There are several approaches such as:

   - Sustained low efficiency daily dialysis (SLEDD)
   - Sustained low efficiency daily diafiltration (SLEDD-f)
   - Extended daily dialysis (EDD)

What all the approaches have in common is that these processes achieve lower solute clearance than intermittent methods but can be administered with less logistic support and significant cost advantage. Also, these therapies can be given with adapted conventional dialysis machines.

Peritoneal Dialysis: Peritoneal dialysis uses the peritoneal membrane as dialysis filter and it is more commonly used in children and in special circumstances in adults. It is very rarely used in AKI patients.

Choice of Optimal Modality:

While starting hemodialysis, the decision regarding the modalities comes into focus. Till now, the literature has not provided any clear-cut answer as to which modality is better[24]. There are some observational studies that denotes that CRRT is associated with better renal recovery due to less haemodynamic instability[25]. Selection of modality should therefore be based upon local expertise and availability of staff and equipment.

IHD has several advantages over CRRT as it can achieve faster blood purification with higher clearance. It is relatively cheap, more widely available in resource poor settings and allows patient mobilization. Due to its shorter duration it allows time for other therapeutic and diagnostic procedures and is less labour intensive and way cheaper than CRRT.

On the other hand, CRRT has some advantages over IHD: The first and overwhelming positive factor for CRRT is that it provides better hemodynamic stability resulting from slower blood flow. It also ensures that it can be given with suboptimal vascular access and does not cause rapid shifts in serum osmolarity.

As an example, in patients with acute brain injury or fulminant hepatic failure, CRRT may be associated with better preservation of cerebral perfusion. On the other hand in case of intoxication with dialyzable drugs or toxins (Lithium, ethylene glycol, methanol), in presence of extreme and life threatening metabolic abnormality or where there is unavailability of expertise or machinery, IHD become the choice. In all other setting CRRT becomes the optimal choice.

Once the decision to give CRRT is taken, several options regarding further specification remain, i.e. CVVH, CVVHD or CVVHDF. The data does not support any modality over the other and the decision is based upon the local expertise available, the device used and the clinician's decision. Middle and larger molecular weight molecules are better cleared with convective therapies than with diffusive therapies. But there are no studies that show improved clinical outcome based on the type of solute transport.

Survival and recovery of kidney function are similar with both CRRT and IHD, and the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for AKI suggest using intermittent and CRRT as complementary therapies in patients with AKI[3].

RRT characteristics that may affect recovery from AKI[4]:

Table II gives an idea regarding the characteristics of RRT and its effect on renal recovery. It is evident that other than a positive fluid balance, there are not many factors that affect renal recovery.

Table II: Characteristic of RRT and its effect on renal & patient recovery

RRT characteristic	Effect on renal recovery	Effect on patient recovery
Modality (intermittent, prolonged intermittent, continuous, peritoneal)*	Intermittent RRT might delay recovery	No effect
Fluid purity and quality standards	Dialysate purity might affect recovery	No effect
Membrane type‡	Bioincompatible membranes might delay recovery	Bioincompatible membranes might affect recovery
Anticoagulation	No reported effect on recovery	Uncertain effect
Haemodynamic stability§	Hypotension might delay recovery	Uncertain effect
Mode of solute clearance (diffusion or convection)	No evidence of effect	No evidence of effect
Ultrafiltration rate	Rapid fluid removal might delay recovery by causing hypotension	No dat
Fluid Balance¶	A positive fluid balance during RRT might delay recovery	A positive fluid balance during RRT might delay recovery
Dialysate temperature	A cooler dialysate temperature might minimize hypotension and promote recovery	No data
Dialysate composition	Higher dialysate sodium concentrations might minimize hypotension and thereby promote recovery	No data
Effect of RRT on other care parameters	RRT might affect drug dosing, nutritional support and nephrotoxin accumulation, which might affect recovery	RRT might affect drug dosing, nutritional support and nephrotoxin accumulation, which might affect recovery
RRT components (for example, access, circuit, fluid composition)	Possible adverse effect	Unknown
Dose/intensity (that is, small solute, clearance)#	Level 1 evidence that intensity of solute control does not affect recovery	Level 1 evidence that intensity of solute control does not affect recovery

*Only association studies; one randomized controlled trial (RCT).

‡Bioincompatible membranes are no longer in use.

§Based on association.

||Small underpowered RCTs.

¶Independent association.

#No effect of small solute control in two large RCTs.

Conclusion:

Despite the high prevalence of AKI patient, there is no specific therapy available as of yet. Management should focus on the underlying causes and correction of metabolic and volume derangements. The preventive measures like volume resuscitation and avoidance of nephrotoxic agents are not always possible in critically ill patients due to presence of sepsis and multiple co-morbidities. Hence RRT remains the cornerstone of therapy when the indications are there.

Early recognition and treatment of AKI is of utmost importance as it can halt the progression of AKI to AKD and ultimately to CKD. With the aim to restore the renal function, the therapeutic targets focus on reinstatement of the circulating volume, prompt relief of outflow obstruction when present and specific treatment of the cause.

Multiple RCTs have proven the fact that prophylactic onset of dialysis before specific indication is rather harmful than beneficial. So the choice remains between delayed and very-delayed onset of dialysis with specific indications to

support the decision making process. As there is no specific threshold for this time frame, clinical judgment and meticulous monitoring become the deciding factor. As more researches are being conducted every day, newer findings and newer techniques are being discovered. With newer development of technology and new advents in therapeutic measures, it is the hope that prevention will become a more plausible idea than invasive measures like renal replacement therapy.

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