Clinical review: Timing of renal replacement therapy

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Abstract

Acute kidney injury is common in intensive care patients and continuous renal replacement therapy is the preferred treatment for this in most centres. Although these techniques have been adopted internationally, there remains significant variation with regard to their clinical application. This is particularly pertinent when one considers that the fundamental questions regarding any treatment, such as initiation, dose and length of treatment, remain a source of debate and have not as yet all been fully answered. In this narrative review we consider the timing of renal replacement therapy, highlighting the relative paucity of high quality data regarding this fundamental question. We examine the role of the usual biochemical criteria as well as conventional clinical indications for commencing renal replacement therapy together with the application of recent classification systems, namely RIFLE and AKIN. We discuss the potential role of biomarkers for acute kidney injury as predictors for the need for renal support and discuss commencing therapy for indications other than acute kidney injury.

Introduction

The primary goal of renal replacement therapy (RRT) is to compensate for, in part, the loss of renal function and associated sequelae. These include the accumulation of nitrogenous waste products, uraemic toxins, electrolyte disturbances, metabolic acidosis and volume overload. Organ support is much beloved by intensivists and, to an extent, defines us, but despite the introduction of convective therapies, RRT has changed little in the past 50 years. Furthermore, the use of current extracorporeal circuits does not compensate for other endocrinological and metabolic functions of the kidney.

The cause of the acute kidney injury (AKI) necessitating RRT is also relevant. The unconditional acceptance of terms such as AKI must be considered together with the underlying aetiology in order to understand the basic pathological processes associated with kidney injury. Without an underlying cause, AKI tells us nothing save an observed disturbance in conventionally measured ‘markers’ of function coupled with reduced urine production. Clearly, the outcome from AKI in a young patient secondary to an interstitial nephritis is very different from that of an elderly diabetic developing AKI following systemic infection from a ruptured viscus. It may be that the aetiology of the underlying condition is also of great import with regard to timing of treatment. In many ways this highlights the differences between single organ ‘AKI’ and ‘multiorgan AKI’ in that timing of RRT on a renal unit may differ significantly from our patients on the ICU in terms of both dose delivered and duration of treatment.

In ICU patients AKI is often encountered at an early stage before traditional measures of renal function are deranged. Therefore, symptoms may not be as pronounced compared to a patient developing renal failure prior to ICU admission. Furthermore, AKI may be regarded as a systemic disease, rather than organ failure in isolation characterised by a systemic inflammatory response with concomitant distant organ injury [1]. Consequently the indication to start RRT in critically ill patients is frequently based on very early signs of AKI, such as prolonged oliguria, rather than conventional markers of chronic kidney disease.

Numerous articles focus on the topic of initiation of RRT in the critically ill and highlight the relative paucity of high quality data, as shown in a recent meta-analysis with only one published randomised controlled trial investigating this issue to-date [2]. This narrative review is intended as a critical reappraisal of the criteria usually applied for initiation of RRT. We wish to outline some of the problems associated with determining relative ‘cutoff’ points for commencing RRT due to the heterogenous nature of the ‘triggers’ used for determining need for renal replacement. We address both initiation and termination of RRT, concentrating on the use of RRT for renal support, although mention is made of other.
indications. A systematic search of the literature was performed using the search terms ‘renal replacement therapy’, ‘haemofiltration’, ‘haemodialysis’, ‘timing’, and ‘initiation’ and, where possible, the following endpoints were extracted: creatinine clearance, glomerular filtration rate, increase in serum creatinine, urine output, markers of tubular injury and mortality.

**Initiation of renal replacement therapy**

**General considerations**

Based on the principle that early goal-directed treatments may improve the outcome of critically ill patients, it may be argued that a similar approach could be applied to RRT. This concept is supported by a hypothesis-generating meta-analysis suggesting that early initiation of RRT in patients with AKI might be associated with improved survival [3]. However, this analysis is hampered by the usual problems, including predominantly retrospective studies and significantly varied endpoints. As recognised from a recent study in chronic kidney disease on the initiation of RRT, it appears that no single parameter, such as estimated glomerular filtration rate (GFR), fulfils an adequate criterion for commencing treatment [4]. Therefore, the composite effect of the accumulation of potentially removable toxins, where non-excreted fluid can also be regarded as a ‘toxin’, rather than any single parameter seems to define the trigger point for intervention.

The conventional parameters used as indicators of renal function (namely urea and creatinine) are relatively non-toxic, with their concentration dependent on volume of distribution, production rate and tubular reabsorption (urea). The volume of distribution for urea or creatinine increases significantly in the volume overloaded critically ill patient [5], leading to lower serum concentrations, although this may not be the same for other, non-routinely measured uremic toxins. Furthermore, the ‘real’ urea volume of distribution may significantly surpass estimated total body water in patients with AKI [6]. Increased production rates of urea in catabolic patients or increased tubular reabsorption in prerenal azotemia may lead to high serum concentrations not paralleled by other toxic waste products. Consequently, serum levels of urea or creatinine may not necessarily reflect the concentrations of uremic toxins and an absolute level of either urea or creatinine cannot, therefore, be acceptable as a defining criterion for ‘early’ versus ‘late’ treatment (Figure 1).

Timing of treatment should not be considered in isolation but together with the treatment dose applied, which, in turn, will determine the time needed until control of uremic waste products is achieved. None of the studies on dose of RRT published recently investigate tailoring delivered dose. It could be envisaged that application of an initial ‘high dose’ followed by a ‘standard dose’ may decrease the time period during which homeostasis is severely disturbed. Adopting the current recommendations regarding RRT, all patients are started with the same minimal dose of 25 ml/kg/h; hence, timing of treatment may be more relevant if the aim of early goal directed therapy in critically ill patients is to minimise exposure of the patient to accumulated toxins (Figure 2).

Approximately 20% of patients develop AKI with the need for RRT late in their admission and this is associated with inferior outcomes [7,8]. However, this criterion (that is, time from admission to ICU until start of RRT) is determined retrospectively and cannot be applied prospectively. Conversely, starting RRT very early results in administration of RRT to patients who would recover spontaneously [9] and thus would never have required this intervention with its associated risks. These include the potential loss of trace elements (for example, selenium) [10], vitamin depletion (for example, thiamine, ascorbic acid), heat loss, nutritional loss (for example, amino acids) [11,12] and infection [13]. Potential benefits of commencing early therapy must also be weighed against potential complications associated with intravenous catheter insertion and exposure to relatively high dose anticoagulation.

**Appraisal of the usual criteria applied in initiating RRT in the critically ill**

Studies examining timing of RRT in the critically ill have to address the criteria used for commencing therapy but this is hampered by the lack of any universally accepted criteria for initiation. Potential candidates include conventional markers of renal dysfunction - urea, creatinine and urine output - but other classical indicators for RRT,
such as refractory volume overload, persistent metabolic acidosis and electrolyte abnormalities, cannot be ignored. Given this heterogeneity, it is of no surprise that consensus as to when to commence RRT has not been reached. In order to try and critically explore this further, we discuss each of these parameters independently.

Uraemia, blood urea nitrogen, and serum creatinine

The development of overt uraemic symptoms is an obvious indication for initiating RRT but treatment on the ICU is rarely, if ever, delayed until full blown uraemia develops. However, early signs such as anorexia, nausea, vomiting or confusion are non-specific and difficult to discriminate from the symptoms of other pathologies present in these patients. Consequently, progressive azotemia is frequently used as an indication to start RRT in critically ill patients developing AKI, although at present no generally accepted threshold based on a definitive urea concentration exists.

The concept of prophylactic haemodialysis for the treatment of acute renal failure (ARF) was introduced by Teschan and colleagues [14] more than 50 years ago, where replacement therapy was started before the development of overt symptoms. Subsequently, data from several retrospective case series as well as two further trials performed in the 1970s and 1980s led to the recommended threshold of blood urea nitrogen (BUN) for the initiation of haemodialysis decreasing to 80 to 100 mg/dl (a urea concentration of approximately 29 to 36 mmol/l) from the previously quoted 165 to 200 mg/dl (approximately 60 to 73 mmol/l) [15-20]. One of the earlier studies examining continuous therapies used a BUN value of 60 mg/dl (approximate to 22 mmol/l) for defining treatment as ‘early’ or ‘late’ [21]. A significant improvement in survival in the ‘early’ group (average BUN of 43 mg/dl at initiation (approximate to 15.7 mmol/l)) was observed when compared to the ‘late’ group (average BUN of 94 mg/dl (approximate to 34 mmol/l)). Another retrospective subgroup analysis on 243 ICU patients with ARF from the Program to Improve Care in Acute Renal Disease (PICARD) study defined early initiation of dialysis based on BUN values below the median value of 76 mg/dl (approximate to 27.7 mmol/l) [22]. The authors found that higher BUN levels on commencing treatment (>76 mg/dl, mean 114.8 mg/dl) were associated with an increased relative risk for death of 1.85 [22]. Interestingly, an increased BUN has been shown to be a ‘biomarker’ for increased mortality in several situations, including acute heart failure [23], coronary artery disease [24], stroke [25], pneumonia [26], bone marrow transplantation [27], acute pancreatitis [28] and following oesophagectomy [29].

Creatinine is considered a better indicator of GFR and was consequently adopted as a parameter for the definition of AKI in whatever guise. Indeed, serial measurements of creatinine demonstrating relatively small increases is an indicator for increased mortality [30,31]. Like urea, creatinine itself is non-toxic and changes in serum concentration may occur independently of the GFR through changes in volume status, altered production, reduced muscle mass or by drug effects on the tubular excretion of creatinine. Consequently, although changes in serum creatinine have been suggested for classifying and staging AKI [32,33], the rate or degree of increase in serum creatinine might not adequately reflect the level of decline of GFR in this setting [34]. Moreover, creatinine levels may be decreased in sepsis due to a reduction in production rate [35].

So what levels of these parameters are considered significant in our everyday practice? Examination of the larger published randomised controlled trials investigating RRT in critically ill patients with ARF with mortality as the end point reveals certain common threads. RRT is usually initiated at BUN levels between 50 mg/dl and 110 mg/dl (approximate to 18 to 40 mmol/l) or a serum creatinine between 3.5 and 5 mg/dl (approximate to 300 to 450 μmol/l), respectively [2,36-41] (Table 1).

Therefore, despite the lack of robust trials supporting particular levels of these parameters in the initiation of RRT in the critically ill, it seems that, as a group, we have devised our own! These reflect current clinical practice but of course may not be the ideal.

Some studies have demonstrated a ‘paradoxical’ relationship between serum creatinine and outcome in patients with AKI and various arguments have centred around these findings, including time between admission and commencement of therapy [42]. These arguments are not new, having been discussed in the literature over a decade.
ago [43-45]. This observation has been explained in various ways, including reduced muscle mass, reduced creatinine production due to sepsis, volume overload and malnutrition, although it probably reflects the length of time elapsed after onset of the condition. Therefore, patients with the lowest determined serum creatinine at the start of RRT have the highest disease burden in terms of need for multiorgan support and, as such, the highest mortality risk; those commencing RRT later with a higher serum creatinine do not. Therefore, the higher serum creatinine as well as any perceived 'delay' in commencing RRT reflects the fact that these patients are in a more favourable group.

**Volume overload and oliguria**

Volume overload due to salt and water retention frequently complicates AKI, occurring in 30 to 70% of ICU patients, and is associated with a greater risk of both morbidity and mortality [46-52]. Indeed, patients who remain responsive to diuretic treatment demonstrate outcome benefits, as do patients exposed to restrictive fluid management in acute lung injury [53,54]. Although diuretics are still frequently employed in order to prevent oliguria [55,56], their use has not been translated into any perceived benefit in AKI [57]. But even if the kidney is still (slightly) responsive to furosemide, ultrafiltration by RRT removes fluid in an iso-isomolal way, that is, without inducing hypernatraemia and alkalosis. Consequently, in the presence of refractory severe volume overload, initiation of RRT appears indicated. Moreover, in the intensive care setting, initiation of RRT is more frequently triggered by oliguria expected to result in volume overload rather than increases in conventional markers such as creatinine or urea [58,59].

A few retrospective studies have investigated early initiation of RRT using a more functional approach (comparing oliguria to conventional measured criteria). Two studies in cardiothoracic patients [60,61] started CRRT when urine output was <100 ml over an 8 hour period whereas a third study [62] used oliguria for more than 12 hours as initiation criterion in patients with septic shock. All three studies showed significantly reduced hospital or 30-day mortality in patients where RRT was started in the presence of oliguria rather than waiting for increases in BUN or serum creatinine. However, the only prospective study to date investigating both delivered dose and early versus late initiation of treatment found no difference between 'early' and 'late' initiation [2]; a caveat is that although well designed, the sample size of this study was relatively small.

**RIFLE and AKIN criteria**

The RIFLE (risk, injury, failure, loss of kidney function, and end-stage renal failure) and Acute Kidney Injury Network (AKIN) criteria [32,33] were introduced to attempt to standardise both the definition and staging of AKI. The obvious advantage of these is that they can combine increasing serum creatinine and decreasing urine output rather than considering just one 'trigger' in isolation. However, a few retrospective analyses, although utilising only creatinine for RIFLE class determination, have shown contradictory results [58,63]. If one translates the urinary output criteria used in the studies mentioned above [60-62] to RIFLE/AKIN classification, this would suggest commencing therapy at either RIFLE Injury or AKIN stage II in critically ill patients when both criteria (urine output and creatinine) are included. To date, however, no trials have investigated the suitability of using RIFLE/AKIN criteria for determining the timing of RRT.

**Electrolyte disturbances**

Potassium homeostasis mainly relies on renal excretion and hyperkalaemia is thus commonly encountered in AKI. Additional factors contributing to hyperkalaemia in critical illness include pH-dependant shifts from...
the intracellular space and relative insulin resistance. Furthermore, rhabdomyolysis, haemolysis and the adverse effects of certain drugs (for example, ACE inhibitors) may also contribute to hyperkalaemia. Untreated hyperkalaemia is fatal, although classical pharmacological 'manipulation' of potassium levels are just that, providing transitory improvement through potassium shifts. The only effective measures that decrease whole body potassium load are diuretic therapy, enteric potassium-binding resins and RRT. Haemodialysis is the most effective way to remove potassium due to the substantially higher potassium clearance (removing 50 to 80 mmol potassium in a 4 hour session [64]) compared to continuous forms of RRT, although continuous venovenous haemodiafiltration, where sufficient total solute effluent rates are achieved, can be used. A specific threshold for initiation of RRT in hyperkalaemia cannot be recommended because this depends on the acuity of serum potassium changes and the observed physiological effects on the patient. Usually, RRT is not commenced at serum potassium values below 6.5 mmol/l where this is the sole indication [65].

Both hyper- and hyponatraemia do occur in AKI, being dependent on volume status as well as any remaining effective free water clearance by the kidneys. If some residual renal function remains, it is rarely necessary to start RRT to correct dysnatraemias, although RRT may be used as an adjunct to therapy.

While less common, severe hypercalcaemia, hyperphosphataemia, hypermagnesemia and hyperuricaemia may be indications for RRT. Severe hypercalcaemia may occur in the setting of hyperparathyroidism or malignancy and can lead to crystal nephropathy, tubular obstruction and subsequent renal failure. In addition to pharmacological treatments including bisphosphonates, RRT may be considered as a last resort treatment for acute hypercalcaemia [66]. In this case, the use of citrate anticoagulation with reduced calcium replacement or calcium free dialysis is highly effective.

**Metabolic acidosis**

The kidney plays a major role in acid-base regulation. Renal failure results in increasing levels of plasma organic acids and other unmeasured anions through continued fixed acid production of around 50 to 100 meq H+\text{/}day [67-69]. RRT plays a major role in acid-base regulation in two ways, firstly by removing metabolic acids and secondly by the net addition of sodium bicarbonate. High anion gap acidoses secondary to poisoning, such as ethylene glycol intoxication, are an indication for acute haemodialysis with both haemodiafiltration as well as extended haemodialysis controlling acidosis in such scenarios [70].

Studies on the use of bicarbonate buffered haemofiltration in lactic acidosis, defined by a blood lactate of at least 5 mmol/l accompanied either by an arterial pH <7.2 or need for more than 60 mmol NaHCO3 per hour to maintain a stable arterial pH, did demonstrate control of acidosis [71]. These criteria were used in part to initiate RRT, although no clear studies exist that define the exact threshold whereby RRT can be started in metabolic acidosis with translation into clinical benefit or show that RRT alters the clinical outcome in the absence of reversal of the underlying cause of lactic acidosis. Practically, an intractable acidosis is usually considered as an indication to commence RRT.

Furthermore, metabolic acidosis increases ventilatory demands and high minute volumes to correct pH. By correcting metabolic acidosis, RRT may protect the lungs against ventilation-induced lung injury.

**Biomarkers**

The recent literature has seen an expansion in studies examining potential ‘biomarkers’ for the early detection of AKI. Candidate molecules include Neutrophil gelatinase-associated lipocalin (NGAL), Kidney injury molecule (KIM)-1 and Cystatin C, and the list continues to grow, although the quest for the renal ‘troponin’ has been hampered by a desire for one biomarker to be seen as superior over others. NGAL, a ubiquitous 25-kDa protein covalently bound to gelatinase from human neutrophils whose expression is increased in the presence of inflammation and epithelial damage, has received most attention in the literature [72,73]. A recent review from the NGAL meta-analysis investigator group concludes that NGAL appears to be of diagnostic and prognostic value for AKI in critically ill patients, albeit in highly selected populations [74]. To date, demonstration of similarly robust sensitivity and specificity in a heterogeneous ICU population is lacking. The application of biomarkers as indicators for the need for RRT has also been examined, with NGAL shown to be a modest predictor of the need for RRT [75,76]. An alternative approach may be the application of biomarkers to indicate which patients may not need RRT. Although this seems to fly in the face of current perceived wisdom, it may be that biomarkers such as NGAL could help delineate which patients have not had an appreciable renal insult. Therefore, where biomarker levels are low this may translate to lack of an appreciable renal insult. This would not be to the total exclusion of other clinical markers but may provide additional evidence for renal damage or the lack thereof.

The reported conflicting results do not add credence for support of one biomarker convincingly over another as yet, but given that the blanket term AKI does not specify cause of insult, perhaps the quest for one such indicator is naive. One could propose that AKI is not one disease but several under an all encompassing umbrella...
and the idea that one 'biomarker' will fit all is thus doomed to failure, particularly when one considers that different biomarkers reflect different pathophysiological processes - for example, serum cystatin and glomerular filtration, NGAL and inflammation, urinary KIM-1 and proximal tubular injury - and that tubular damage does not always translate into a reduction in clearance.

More research will answer these questions and if suitable biomarkers are found, then this may prove to be an exciting time in critical care nephrology. One may envisage clinical trials aimed at early intervention in specific forms of AKI that may alter the course of the process: but will they provide a basis for early RRT? Only time will tell.

'Door-to-RRT time'

Prompt dialysis after admission has been shown to reduce mortality in certain conditions, such as leptospirosis, resulting in the concept of aiming at a short 'door-to-dialysis time' [77]. Some retrospective analyses [7] have employed the time after ICU admission as the definition of timing (that is, early versus late) of RRT, although this is susceptible to several errors. Firstly, it is retrospective, and secondly, AKI may occur on admission or later during the ICU stay. Several studies show that 'early AKI' has improved outcomes over 'late AKI' [8,9]. It may be that early AKI includes those with 'transitory AKI', which has a significantly better prognosis [9]. Finally, starting RRT in early AKI may include patients who would recover spontaneously, and improved outcome will thus be expected. Indication that very early initiation of RRT may be harmful was demonstrated by a prospective randomised trial on patients with severe sepsis [78]. Delayed weaning from mechanical ventilation or vasopressors together with increased mortality was observed compared to standard medical treatment.

Non-'renal' indications for renal replacement therapy

Severe sepsis and septic shock are associated with AKI in up to 50% of patients, although classical indicators of AKI are often not elevated initially [79]. Consequently, other criteria such as prolonged oliguria or severe metabolic acidosis may be sufficient indication to commence RRT [62]. There remains a theoretical hypothesis that removing inflammatory mediators associated with sepsis could translate into patient benefit. Such 'prophylactic' RRT remains attractive but the only prospective randomised study investigating this failed to demonstrate any beneficial effect of RRT in severe sepsis without AKI [80]. As mentioned, early RRT in sepsis may even be harmful [78]. Thus, on the basis of current evidence, such a procedure cannot be recommended routinely [81].

The use of extracorporeal circuits is also associated with significant blood cooling, which is considered an unwanted side effect during routine RRT but may be beneficial in intractable hyperthermia, such as malignant neuroleptic syndrome, malignant hyperthermia and heat stroke. Case reports of cooling by extracorporeal circuit do exist for all forms of intractable hyperthermia [82]. Indeed, a randomised prospective study reports a favourable outcome in patients after cardiopulmonary resuscitation when applying high volume haemofiltration, either at 37°C or with cooling [83], but the advent of alternative means of cooling, either externally or by adapted central venous catheters incorporating a cooled water circuit, has superseded the use of extracorporeal circuits.

Dialysis following overdose of dialysable drugs or toxins is another indication for RRT. Drugs that can be effectively dialysed are characterised by their water solubility, low protein binding, low molecular weight (<500 Da) and small volume of distribution. Thus, RRT may be considered in cases of overdose or intoxication with certain alcohols (for example, methanol, ethylene glycol), salicylate, lithium, theophylline or methotrexate [84]. Extended dialysis has also been described as being successful in parquat intoxication, although haemoperfusion appears more effective [85].

Rhabdomyolysis through whatever cause results in the release of myoglobin, leading to AKI through vasconstriction, tubular cell damage by oxidant injury and tubular obstruction by myoglobin casts. Rhabdomyolysis and myoglobinuria are responsible for about 5% of ARF in the USA [86] and RRT is typically initiated after the failure of more established measures, including alkaline-fluid hydration, mannitol and diuretics. Early initiation of RRT for myoglobin removal in severe rhabdomyolysis accompanied by acidosis and volume depletion is recommended by some authors [87], although conventional membranes have sieving coefficients for myoglobin within the range 0.4 to 0.6. In order to increase efficiency of myoglobin clearance, the use of super 'high flux' membranes may be employed [88], although 'prophylactic' removal of myoglobin by dialysis has not been demonstrated to change the clinical course.

Radiocontrast nephropathy remains a prominent cause of hospital-acquired AKI and is still associated with significant mortality [89]. Contrast nephropathy is a complex disease, especially in the cardiac patient, where it comprises the acute cardiac events compromising cardiac function, the negative inotropic effects of the contrast medium, pulmonary congestion due to cardiac disease, hydration-related fluid overload and underlying renal insufficiency compromising fluid removal by the kidney. It seems more appropriate, therefore, to talk about contrast-associated nephropathy than contrast-induced nephropathy. RRT before and after contrast
interventions may be considered in patients with more severe underlying renal insufficiency who may not tolerate hydration, may need high contrast volumes or are at risk for contrast-induced cardiac decompensation [90,91].

Termination of renal replacement therapy

To date, no clearly defined criteria for the termination of RRT have been established. Usual practice is to introduce intervals without RRT and await signs of spontaneous recovery. Two retrospective trials investigating this found urinary output the best predictive parameter for cessation of RRT. The Beginning and Ending Supportive Therapy for the Kidney (BEST kidney) study defined a threshold of 450 ml/day as predictive for not requiring further RRT [92]. Similarly, an increased risk of recommencing dialysis was found for postoperative patients with a urinary output <100 ml/h [93].

Conclusion

RRT should undoubtedly be initiated in case of life-threatening conditions such as refractory hyperkalaemia, acidosis, fluid overload and uremic symptoms, including refractory uremic bleeding or pericarditis. However, there is a broad consensus that RRT should be initiated - if possible - before uremic symptoms develop. Initiation should consider the degree of other organ failure, the presence of harmful conditions that can be modified by RRT (acidosis, fluid overload), the change of serum creatinine or urea in relation to fluid balance reflecting renal recovery or not, and the clinical estimate whether renal function will recover soon or not (recovery or persistence of other organ failure, especially vasopressor-dependent circulation). Absolute concentrations of urea and creatinine are not decisive.

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