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EDITORIAL

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Haste makes waste—Should current guideline recommendations for initiation of renal replacement therapy for acute kidney injury be changed?

Abstract

There is broad consensus among guideline organizations that renal replacement therapy (RRT) should not be delayed in case of life-threatening conditions. However, in case of severe acute kidney injury (AKI) without these conditions, it is unclear whether immediate RRT has an advantage over delayed RRT. Two recently published randomized controlled trials (AKIKI and ELAIN) with seemingly opposite results have reignited the discussion whether guideline recommendations on initiation strategies in severe AKI should be adapted. This editorial discusses RRT initiation strategies in severe AKI, based on recent literature and highlights the potential advantages and disadvantages of immediate vs delayed start. Overall, evidence in favor of immediate compared to delayed strategies is sparse and there is wide heterogeneity across studies making it difficult to draw firm conclusions. RRT should not be delayed in case of refractory hyperkalemia, severe metabolic acidosis or pulmonary edema resistant to diuretics. In all other cases, a delayed strategy seems justified and might enhance renal recovery. RRT is not a "it doesn't hurt to try" technique and can expose the patient to a higher risk of bleeding, hemodynamic problems, under-dosing of antibiotics, loss of nutrients, catheter-related complications and the uncertain effects of blood-membrane interactions. There is no compelling reason to change current guideline recommendations and research focus should shift toward the development of algorithms as a decision aid tool for RRT initiation in severe AKI.

1 | INTRODUCTION

The annual incidence of acute kidney injury (AKI) managed with renal replacement therapy (RRT) has increased over time,[1] and currently about 8%-12% of ICU patients receive RRT.[2] This increase may reflect changes in either the occurrence of severe AKI or practice shifts in the thresholds for initiating RRT. The decision to start RRT is unequivocal in the presence of life-threatening AKI complications, but in their absence the optimal timing of RRT initiation for AKI remains uncertain, in particular since 2 recently published randomized trials showed seemingly opposite results.[3,4] This has reignited the discussion whether or not early start has a benefit over late start of RRT in AKI.

The decision to start RRT can, in these circumstances, be driven by a number of factors such as clinical symptoms, serum solute levels, severity of AKI, prognostic scores, number of failed organs, and even availability of equipment and personnel.[5] This results in a wide variety of indications for and differences in prevalence of AKI requiring RRT. This discrepancy in indications also blurs interpretation of differences in outcome between studies and institutions.

This editorial discusses recent trials comparing early/immediate vs late/delayed RRT and provides a background summary for clinicians involved in making decisions on RRT initiation, irrespective of the modality offered (intermittent hemodialysis, peritoneal dialysis, continuous RRT, or slow extended hemodialysis). Specific conditions where hard indications for RRT other than just AKI can be considered, such as acute tumor lysis syndrome, severe rhabdomyolysis, or intoxications with toxic alcohols, lithium, salicylate, theophylline or valproate, will not be covered.

2 | WHAT DO THE GUIDELINES SAY?

There is broad consensus among guidance bodies that RRT should not be deferred in what are called "life-threatening conditions".[6-10] Most guidelines explicitly state that clinicians should consider the broader clinical context, the presence of conditions that can be modified by RRT, and trends of laboratory tests rather than single thresholds when making the decision to start.[11] However, there seems to be no consensus on what exactly is meant by "life-threatening conditions," and what the thresholds of laboratory parameters should be. Table 1 lists some of these parameters and their suggested thresholds.[12,13] It is clear that for most of these criteria, hard evidence to support their validity is lacking, since they are based on incorrect extrapolations from observational studies, thus mixing cause and consequence.

For example, data demonstrating an association between dismal outcome and hyperkalemia are largely retrospective.[14] In a study by McMahon et al,[15] potassium concentrations at ICU admission and duration of hyperkalemia are strong predictors of all-cause mortality with a significant risk gradient across serum potassium strata, but this is probably explained by the association of hyperkalemia itself with worse disease conditions. The use of RRT for management of

TABLE 1 Currently accepted "conventional" or "absolute" indications for initiation of renal replacement therapy

Parameter	Definition
Hyperkalemia	Serum potassium ≥6.5 mmol/L, or rapidly rising potassium, or refractory to standard supportive medical management
Metabolic acidosis	pH ≤7.15
Uremia	Urea >36 mmol/L (BUN = 101 mg/dL, blood urea = 216 mg/dL)
Oliguria or anuria	Urine output <0.3 mL kg^{-1} h^{-1} for ≥24 h or anuria for ≥12 h
Fluid overload	Pulmonary edema not responding to diuretics and defined by the presence of all of the following factors: 1. >10% fluid accumulation (cumulative fluid balance/baseline weight >10%) 2. oliguria (urine output <0.5 mL kg^{-1} h^{-1} for ≥12 h) and 3. Severely impaired oxygenation (PaO^2/FiO^2 < 200 indicated by respiratory Sequential Organ Failure Assessment (SOFA) score ≥3)

hyperkalemia has not been associated with improved survival, whereas more conservative treatments such as IV calcium or insulin/dextrose are.[14,16] The underlying explanations are complex ranging from the fact that RRT is indeed inferior, from higher complication rates for RRT wiping out potential benefits, from the perils of a too rapid correction of potassium, from more sick patients receiving RRT (selection bias) or from RRT being the last resort (indication bias). Further studies should explore the mechanisms underlying these observations.

Similarly, no studies exist delineating a clearly defined threshold for initiation of RRT in AKI patients with metabolic acidosis; studies are needed which examine improvement of clinically relevant, rather than surrogate, outcomes. However, in the absence of severe respiratory acidosis, a pH below 7.15 with an intractable metabolic acidosis is a generally accepted indication for RRT.

Uremia, often assessed by measurement of serum urea, is itself commonly used as an indication to start RRT. However, urea is not an ideal marker, as its generation and volume of distribution are highly variable in critically ill patients. At present, no generally accepted threshold based on a definitive urea concentration exists. Substantial azotemia [suggested by urea concentrations >30 mmol/L (BUN 84 mg/dL) or creatinine concentrations >300 μmol/L (3.4 mg/dL)] is judged a marker of an undesirable toxic state. However, no recommendations indicate what severity of acute azotemia can be tolerated. We agree with Bellomo et al[17] that this degree of azotemia should probably be treated with RRT unless recovery is imminent or already under way, or a return toward normal urea and creatinine concentrations is expected within 24-48 hours (eg, in transient AKI) such as is seen with severe volume depletion.

In case of metabolic derangements, it is also important to consider that some patients are more vulnerable than others due to the presence of certain comorbidities. Such derangements should be considered in the decision to initiate dialysis.

Multiple studies have demonstrated that the severity of volume overload at initiation of RRT is a strong predictor of mortality.[18,19] There is general agreement that in AKI patients volume overload with pulmonary edema resistant to diuretics is a formal indication for initiation of RRT and ultrafiltration.[17]

3 | WHAT ARE THE POTENTIAL ADVANTAGES AND DISADVANTAGES OF STARTING RRT EARLY VS LATE?

Early/immediate initiation strategies could theoretically be advantageous because of more rapid equilibration of acid-base status, avoidance of cardiac arrhythmias, and easier control of fluid balance. So far, however, no study has evaluated the attributable mortality of RRT requiring AKI. This attributable mortality is the number of deaths due to the presence of AKI itself rather than any associated or underlying comorbidities. This is of importance in the discussion on timing of start of RRT, as the attributable mortality is the maximum to be gained with the treatment being 100% effective and having no side effects. Outside of the conditions associated with "hard" indications to start RRT, the causal impact of AKI on mortality is presumably low. Studies indicate that only patients with AKI complications have a better survival when RRT was initiated.[20]

Therefore, it seems unlikely that a broader application of RRT would have any significant impact on mortality.[21] In addition, dialysis is not a "it doesn't hurt to try" technique and can expose the patient to a higher risk of bleeding, under-dosing of antibiotics, loss of nutrients and catheter-related infectious and noninfectious complications. Recovery of renal function can be jeopardized, partly due to higher risk of hemodynamic instability during RRT. Such instability may also have cardiac and neurologic complications. Rapid correction of acidosis can enhance a further decrease in calcium levels causing arrhythmia. The consequences of blood-membrane interactions are uncertain but may well be harmful. Especially in CRRT, there is a risk for development of hypophosphatemia which can lead to muscle weakness and prolonged respiratory failure which is associated with higher mortality.[22-24] In observational trials, use of RRT is independently associated with mortality.[20,21,25-28] A too early start can thus be harmful.[29]

4 | TRIALS ON EARLY VS LATE START OF RRT

Until recently, we mainly had to rely on data from retrospective studies[30-33] comparing early vs late RRT. Although these studies

generally favored an early start, the paucity of RCT's[34-37] and the heterogeneity across studies made it difficult to draw firm conclusions. Several meta-analyses,[38,39] mainly of retrospective studies, concluded that there was a potential benefit for early start of RRT. However, these meta-analyses were biased by mixing up observational and randomized studies with great heterogeneity across studies. One of the major contributors to the heterogeneity was the varying definition of "early" vs "late" with time factors, clinical factors or biochemical factors all being used. Another problem in observational studies is the immortal time bias induced by excluding patients who recover renal function before RRT is needed, rather than considering them as "late starters". In excluding these patients with an excellent prognosis from the analysis, the outcome of the delayed RRT group is penalized.

Since the publication of these meta-analyses, several randomized controlled studies have appeared that do not support the concept that early RRT is beneficial[40-44] and a more recent meta-analysis[45] including these studies, does not support the conclusion of the previous meta-analyses.

In 2016, 2 RCT's (the ELAIN and AKIKI trial)[3,4] on immediate vs delayed RRT were published, with seemingly opposite results. Both studies were intention-to-treat and thus also included in the analysis patients who were randomized but had no need to be started on RRT. However, these studies were very different in their approach.[46,47] The ELAIN study included patients with predominantly postsurgical KDIGO stage 2 AKI and either septic shock or refractory fluid overload. RRT modality and dose were defined as continuous veno-venous hemodiafiltration (CVVHDF) at 30 mL kg^{-1} h^{-1} with 100% predilution and 1:1 ratio of dialysate to replacement fluid. Patients randomized to the early start group were started on dialysis within 8 hours after inclusion. Patients randomized to the delayed start group were only started on RRT within 12 hours of reaching KDIGO stage 3. In the latter group, over 90% of patients with stage 3 KDIGO AKI were eventually treated with RRT. This is no surprise, as almost 75% of patients were diagnosed with fluid overload or worsening pulmonary edema and had thus in fact a "hard" indication to start RRT already *before* randomization. One could thus summarize that ELAIN investigated the effect of delaying dialysis in those who really needed it. It is thus not surprising that the conclusion of the ELAIN study was that an early vs delayed start improved patient outcome.

In contrast, the AKIKI trial excluded patients with established criteria to start dialysis, such as severe hyperkalemia or pulmonary edema. Patients not meeting exclusion criteria were included from the moment they reached KDIGO stage 3. Dialysis modality was mixed intermittent and/or continuous RRT and the dialysis dose was at the discretion of the treating physician. Patients randomized to the early group in the AKIKI trial were started on RRT within 6 hours of randomization whereas those randomized to the delayed start group were only to be started on RRT whenever they met one of the predefined "absolute" criteria. AKIKI showed no superiority for early initiation of RRT. In the delayed start group, RRT was avoided in around 50% of patients (vs only in 9% in the ELAIN trial). In a recent post hoc analysis of this trial,[48] subgroups of patients with sepsis, ARDS and tertiles of baseline illness severity score were investigated. Results confirmed that there was no advantage for an early dialysis initiation strategy in these subgroups.

What do these studies teach us? Most important, the terms "early" vs "late" should better be replaced by "immediate" and "delayed" RRT, and should be based on well-established criteria rather than classification criteria or biomarkers. Next, RRT should not be deferred in those who really need it. As described above, the only absolute indications for dialysis therapy in severe AKI are significant volume overload refractory to diuretics, refractory hyperkalemia and refractory metabolic acidosis.[49] In the absence of these criteria, a "wait and see" approach is justified. When making a decision, one should not focus on specific thresholds but take a holistic view on the patient's clinical condition. Instead of eagerly awaiting the results of further trials comparing early vs late (eg, IDEAL-ICU[50] and STARRT-AKI[51]), the research community should focus on developing algorithms to help clinicians in their decision making and elucidate the underlying behavior/attitudes that drive decision making to start dialysis.[52]

5 | CONCLUSION

When life-threatening conditions are present, RRT should not be delayed. In all other cases, an "expectatio armata" approach seems justified. There is no hard evidence that, in the absence of established criteria, early start of RRT improves outcome. RRT is not a harmless intervention and starting too early imposes unnecessary risks to the patient and might jeopardize renal recovery. The focus of research should shift to developing algorithms helping clinicians in their decision-making process.

CONFLICT OF INTEREST

None.

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