Seminars in Dialysis

Unnecessary Renal Replacement Therapy for Acute Kidney Injury is Harmful for Renal Recovery

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ABSTRACT

The use of renal replacement therapy (RRT) for severe acute kidney injury (AKI) is frequently necessary in the face of life-threatening complications; however, there is wide practice variation with respect to triggers for RRT initiation. Recent evidence suggests that RRT may be independently associated with impaired recovery following AKI. There are plausible mechanistic reasons why RRT may be harmful and this concept is supported by ancillary evidence in the form of studies that have assessed the impact of different modalities of RRT for AKI as well as some of the literature pertaining to initiation of chronic hemodialysis in end-stage kidney disease patients (ESKD). As such, avoiding unnecessary RRT (URRT) is a desirable goal. There is emerging evidence of strategies that may be effective to help limit URRT. These strategies primarily involve early identification of AKI and limiting iatrogenic harm once AKI is established. Further research into defining and preventing URRT may help improve the consistently poor outcomes following severe AKI with respect to development of chronic kidney disease and ESKD.

Acute kidney injury (AKI) occurs commonly among hospitalized patients (1,2) and for those who require renal replacement therapy (RRT), mortality can be excessive (3,4). Among survivors, many never recover sufficient function to wean from acute dialysis and are left with end-stage kidney disease (ESKD) (5). Incomplete or "partial" recovery is also now recognized as a common survivorship complication after an episode of AKI, even among those with normal baseline renal function. The loss of "renal reserve" and evidence of persistent kidney damage or even overt moderate to severe chronic kidney disease (CKD) has been described in as many as 40% of survivors several years after AKI (6,7).

Recent observational studies suggest that even those who completely recover kidney function following AKI, defined as a return to baseline or near baseline serum creatinine, remain vulnerable to developing downstream incident CKD or accelerated progression to ESKD (8,9). Consistent with these findings, animal studies have demonstrated pathologic changes predisposing to future CKD persist despite apparent "functional" renal recovery in experimental models of AKI. These observations may herald the significant loss of nephron mass and diminished renal reserve predisposing to accelerated progression to CKD.

At the present time, in the absence of large, high-quality prospective studies in humans, the exact nature of the relationship between AKI and CKD has yet to be fully characterized (10). Nonetheless, there is sufficient evidence to support the paradigm that AKI can predispose to CKD in a bi-directional manner (11) and that the likelihood of recovery is diminished as AKI severity increases (12–14). In this sense, "severity" could represent not only a greater magnitude of acute insult but also a sustained insult with a prolonged duration of AKI and recurrent episodes of acute injury where there is insufficient intervening time for recovery—all of which will reduce the likelihood renal repair and recovery (15).

Measures to limit the impact of severity, duration, and frequency of AKI are most likely to be effective when instituted upon detection of early "incipient" AKI (16). Once a patient develops overt AKI, the therapeutic focus shifts to the elimination of the inciting injury stimulus, limiting further kidney damage, avoiding serious complications of reduced kidney function, and facilitating repair and recovery. Among those critically ill or those with

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overt kidney failure, RRT is often initiated to support organ function pending recovery (4). While RRT can readily reverse life-threatening metabolic derangements and fluid overload, various aspects of how RRT is operationalized may negatively influence the course of AKI and probability of renal recovery. In addition, the unnecessary exposure to RRT in AKI among those without life-threatening complications or in the setting when there is a high likelihood of recovery may delay or disrupt the recovery process.

Renal Replacement Therapy: Harmful for Renal Recovery

Rates of RRT utilization for AKI have increased over the last decade (17,18). This finding may be partly attributable to demographic and case mix transition, along with shifting standards of practice in response to observational data suggesting improved outcomes with earlier RRT initiation (18). Nonetheless, when considered in isolation from the timing of RRT initiation, recent observational data have suggested that use of RRT in AKI may be independently associated with an increased risk of death (19,20).

Mechanisms of Harm—Intradialytic Hypotension and Beyond

In a 1990 article published in this journal, Conger asked: "Does Hemodialysis Delay Recovery From Acute Renal Failure?" (21). He noted that, for some of the earliest ever hemodialysis (HD)-treated patients, all of whom had AKI secondary to trauma, pathologic studies showed evidence of fresh tubular necrosis in the kidneys of those with delayed renal recovery (21). The sustained duration of AKI and kidney function loss after the inciting trauma was attributed to repeated episodes of relatively mild and transient intradialytic hypotension (21). Proponents of using CRRT over intermittent HD have long suggested that the higher likelihood of hemodynamic instability associated with IHD could be harmful, potentially reducing the likelihood of renal recovery (22). In the non-AKI population on chronic hemodialysis, hypotension and myocardial stunning occur frequently while patients are receiving treatment, even in the absence of underlying cardiovascular disease (23). As well, the occurrence of hypotensive episodes in incident chronic HD patients in the first 3 months of HD has been shown to correlate with loss of residual renal function (24). While the aforementioned studies focused on intermittent HD, it is important to recognize that CRRT and slow low-efficiency dialysis (SLED) may also be associated with episodes of hypotension if prescribed and operated erroneously (4,25). The Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Study reported that hypotension related to CRRT occurred in 19% of 1006 patients treated with CRRT (4). However, continuous modalities such as CRRT are associated with less hemodynamic instability as they allow for more gradual ultrafiltration and reduce the intensity of osmotic shifts that may precipitate hypotension. As such, Conger's suggestion from almost 25 years ago could logically be expanded to encompass any form of RRT used in the treatment of AKI.

In addition to the potential for inducing hypotension, the use of RRT is associated with a unique constellation of treatment-related complications (recently reviewed in more detail elsewhere; 22,26) that may impact negatively upon recovery from critical illness and, as a result, the course of longer-term renal recovery. These include:

Complications Related to Vascular Access

To initiate RRT for AKI, the establishment of vascular access with either a temporary or tunneled hemodialysis catheter carries the risk of mechanical and infectious complications (27). These complications may worsen critical illness and AKI severity, lessening the likelihood of renal recovery.

Subtherapeutic Levels of Essential Medications

RRT complicates medication prescription and dosing (28). Appropriate antibiotics are potentially life-saving in septic shock (29) and infections are the leading cause of death in those with AKI; (28) however, medication dosing in AKI and during RRT for AKI has been suboptimally investigated, in particular for CRRT and SLED (28). Notably, many patients receiving CRRT have evidence of subtherapeutic levels of antimicrobials (30,31).

Depletion of Electrolytes and Micronutrients

RRT may cause excessive depletion of electrolytes, essential nutrients, and trace metals (26). Hypophosphatemia is common during CRRT (32,33) and has been associated with prolonged recovery from critical illness (34). In a post hoc analysis of the RENAL study, hypophosphatemia secondary to RRT was not associated with significantly increased mortality (35), however, its association with renal recovery has not been the focus of prior study.

Proinflammatory Consequences of Extra-Corporeal Therapy

While AKI itself is associated with increased levels of inflammatory cytokines (36–38), blood contact with the dialyzer membrane during RRT may promote an additional proinflammatory response (26,39). Given that the intrinsic regenerative capacity of nephrons has been shown to be reduced in the presence of ongoing systemic inflammation (40), it is biologically plausible that RRT may disrupt renal

repair and recovery, in particular among patients where RRT could have potentially been avoided.

Evidence that Renal Replacement Therapy is Harmful for Renal Recovery

RRT is undoubtedly effective in reversing the life-threatening complications of AKI, where the risk of providing RRT seems peripheral when compared to the perceived benefit. However, teasing out whether RRT implementation itself is associated with an attributable harm in terms of nonrecovery and/or death is complex (19,20). The challenge would be to measure the isolated contribution to nonrecovery of a particular complication related to AKI (i.e., metabolic acidosis, fluid overload), whereby RRT may be triggered. Such an analysis is made more complex by the recognized wide variation in practice around selection of patients for whom RRT will have a perceived benefit. A direct comparison of those treated or not treated with RRT have proven largely unhelpful, due to treatment selection bias and RRT-treated patients commonly being measurably sicker than those who are not (41,42).

The decision of whether or not to initiate RRT for AKI is closely related to the question of when to optimally start. Although nearly all practitioners would agree that life-threatening, refractory hyperkalemia should trigger RRT, there may not be consensus as to what level of hyperkalemia is truly life-threatening. This can be evidenced in studies that have demonstrated wide practice variation with respect to RRT initiation both between and within jurisdictions (43,44).

When assessing the impact of using RRT to treat AKI versus conservative treatment, wide practice variation does, to some extent, uncouple the influence of illness severity. A secondary analysis of an RCT comparing IHD to CRRT included a total of 1303 patients with AKI from nine Belgian intensive care units (ICUs) (20). Of those, 650 patients were treated with RRT. As initiation of RRT in this study was left to the clinician's discretion, wide variation in RRT utilization (and mortality) was observed across sites and RRT utilization did not correlate with illness severity. After limited adjustment for covariates including illness and AKI severity, the risk of death was significantly increased with RRT compared to conservative treatment (relative risk, RR: 1.75 [95% CI: 1.4–2.3]) (20). Illness and AKI severity was assessed using the Stuivenberg Hospital Acute Renal Failure (SHARF) score, developed and validated (45,46) in the same setting where the study was performed. Additional adjustment for other illness severity measures (Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA)) as well as age, comorbidities and the cause of AKI, did not alter the finding that RRT usage was an independently associated with higher mortality. In terms of renal recovery, the trend was similar with dialysis-dependence (or eGFR <15 ml/minute) at time of hospital discharge being more likely among those treated with RRT (24%) compared with those treated conservatively (9%) ($p < 0.001$) (20). Regardless, given the mechanistic plausibility that RRT may be harmful in certain circumstances, at the very least, these findings invoke the concept that "unnecessary" RRT (URRT) in AKI should be avoided.

The ATN (33) and RENAL (32) studies were large RCTs that compared higher intensity versus lower intensity RRT in patients with AKI. These studies employed different strategies in terms of the RRT modalities that were used. In the ATN study, continuous renal replacement therapy (CRRT) was used when patients required vasopressors and intermittent hemodialysis (IHD) was used when they were hemodynamically stable. Patients were transitioned between modalities according to their hemodynamic status on an ongoing basis (33). In contrast, patients in the RENAL study were treated exclusively with CRRT while in the intensive care unit (ICU) regardless of hemodynamic stability (32). Bellomo and Schneider (22) noted that the discrepancy in renal recovery rates between ATN and RENAL (25.8% versus 8.0%) might be explained by this different approach to modality selection given the similarities in baseline patient characteristics and case mix between the trials (47).

Further support for the idea that initial treatment with CRRT may result in greater likelihood of renal recovery when compared with IHD can be found in a recent, large retrospective cohort study conducted by Wald et al. (48). This study matched 2004 patients who received CRRT as their initial treatment for AKI with an equal number of patients who received IHD as their initial treatment for AKI according to propensity scores for initiation of CRRT developed using a comprehensive multivariate model (48). Over a median 3 years of follow-up, the risk of requiring chronic dialysis was significantly reduced for patients initially treated with CRRT with a hazard ratio of 0.75 [95% CI, 0.65–0.87] (48). The major limitation of this study again relates to the possibility of residual confounding and, in particular, confounding according to treatment intention.

While a suitably designed RCT may be the only definitive way to answer the question of whether or not the choice of RRT modality has a significant impact upon renal recovery, Bellomo and Schneider (22) have argued that, given the logistical challenges of conducting such an RCT, a change in practice favoring the initial use of CRRT for AKI, regardless of the hemodynamic status of the patient is warranted on the grounds that it may reduce the likelihood of CKD and ESKD, if not necessarily mortality (22).

There is likely a spectrum of risk/benefit in which CRRT is preferable to IHD; however, either may still be more harmful relative to avoiding RRT altogether in situations when RRT is not necessary.

Avoiding Unnecessary Renal Replacement Therapy

Avoiding URRT is clearly desirable, both from the perspective of patient safety and health resource utilization (49). Unfortunately, our capacity to reliably predict which patients with AKI are likely to worsen and need RRT is relatively poor. Furthermore, there is a paucity of high-quality evidence to inform clinical decision support on the optimal circumstances to start RRT, predisposing to wide variations in practice. Accordingly, there will be patients who receive RRT for AKI when it may not have been necessary, not deemed beneficial and/or not deemed a suitable use of resources (50). Further studies are needed to minimize URRT by enabling more precise identification of patients who are unlikely to benefit.

Fluid overload is a common indication for starting RRT and numerous observational studies have shown that the degree of fluid accumulation in critically ill patients with AKI is associated with increased mortality (51–53). In addition, it has been reported that fluid overload at the time of initiation of RRT is associated with decreased likelihood of renal recovery (54). Taken together, these observations suggest that it might be beneficial for renal recovery (and more importantly, survival) to initiate RRT to prevent progressive and/or excessive volume accumulation that is resistant to conventional diuretic therapy. However, in the absence of RCT-level data, it remains unclear whether fluid overload is responsible for poor outcomes or merely present as a confounding marker of illness severity (55). As such, the practice of initiating RRT to prevent complications of fluid accumulation in the absence of fluid overload remains in need of higher quality evidence. More broadly, limiting use of RRT in situations in which it has not been shown to be beneficial, such as for when used as an adjunctive treatment for sepsis, would reduce URRT.

Preventing lapses in safety may reduce the need for URRT. For example, ensuring that a patient with AKI and an elevated potassium level is provided with a low potassium diet may allow time for renal recovery to occur and avoid the need for RRT on the basis of hyperkalemia. In the United Kingdom, the 2009 National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report entitled "Adding Insult to Injury" assessed the quality of care provided to patients who died in hospital with a primary diagnosis of AKI (56). It found that 154 of 529 patients (29%) had AKI inadequately clinically managed. This included 85 patients (16%) who were inadequately volume resuscitated when it was indicated for prerenal AKI and 36 (7%) for whom nephrotoxic drugs were improperly continued (56). Notably, there were delays in the identification

TABLE 1. Strategies to reduce unnecessary renal replacement therapy.

Strategy	Method	Specific Technique(s)
Limiting AKI Progression	Early recognition of AKI	Alerts via eCIS / EMR (57–59) to spur appropriate work-up and management, including: • relief of obstruction for postrenal AKI • appropriate fluid resuscitation for prerenal AKI • avoidance of nephrotoxins • avoidance of contrast
	Enhanced monitoring of early AKI	Alerts via eCIS / EMR (57–59) to ensure timely follow-up serum creatinine testing to enable appropriate ongoing management, e.g., avoiding unnecessary contrast exposure in context of worsening AKI
	Avoidance of nephrotoxins (60)	Alerts via eCIS / EMR (57–59) to: • discontinue or prevent starting nephrotoxic medications (or using procedures using contrast)
	Appropriate intravenous fluid selection	• Avoidance of chloride-rich solutions (16) • Avoidance of hydroxyethyl starches (61)
Allowing time for recovery prior to an indication for RRT developing	Preventing fluid overload (16,54)	• Appropriate use of diuretics • Judicious fluid administration • Low-salt diet when appropriate
	Limiting potassium intake	• Low potassium diet when appropriate • Avoiding use of potassium containing intravenous solutions or oral supplements
Restricting the application of RRT in selected circumstances	Not using RRT for nonevidence-based, "off-label" indications	• Not using RRT for sepsis or pancreatitis in the absence of other indications. • Not using RRT prophylactically (e.g., prevention of volume overload or hyperkalemia).
	Limiting use of RRT in patients who are very unlikely to benefit (50)	Not using RRT for: • Patients extremely likely to die soon after starting RRT, using the potential initiation of RRT as an opportunity to (re)define over all goals of care • Patients who are likely to recover renal function prior to requiring RRT for a life-threatening indication

AKI, acute kidney injury; eCIS/EMR, electronic clinical information systems/electronic medical records; RRT, renal replacement therapy.

of AKI in 42 of the 98 cases (43%) in which AKI occurred postadmission (56). This represents a clear evidence care gap where opportunities to prevent avoidable complications that likely prompt URRT were missed.

For all patients with AKI, emerging evidence suggests that there are a number of strategies, largely focused on prevention of iatrogenic harm, that reduce the likelihood AKI will progress in severity and then result in unnecessary exposure to RRT. These are briefly summarized in the Table 1. A recent report describes the implementation of a fully automated clinical decision support system (CDSS) for early detection of in-hospital AKI (57). As others have suggested (58), further refinements of CDSSs for AKI detection may result in significant improvements to the care of patients with AKI. This may ultimately result in a reduction in the frequency of URRT.

Conclusions

The use of renal replacement therapy (RRT) for severe acute kidney injury (AKI) is often necessary to sustain life but may also be applied unnecessarily. Intradialytic hypotension and other complications of RRT provide a plausible explanation for why RRT may contribute harm, in particular among those where it was marginally indicated. Observational studies have implied, though not consistently, that RRT is independently associated with a decreased likelihood of renal recovery after AKI. These studies highlight that, despite the absence of RCT-level evidence that RRT is harmful unto itself, limiting the use of unnecessary RRT is a desirable goal from both the perspective of the patients and the health system. Emerging evidence suggests strategies involving earlier identification of AKI may help limit unnecessary RRT. In addition, strategies to limit iatrogenic harm once AKI is established and to restrict the use of RRT in situations in which it is unnecessary or where patients are very unlikely to benefit will also reduce URRT. Further research is needed to better define unnecessary RRT and untangle its association with recovery, incident chronic kidney disease and ESKD following AKI.

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