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## Renal Recovery after Acute Kidney Injury

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**Renal recovery after acute kidney injury is affected by co-morbidities as well as ICU treatment. Nephrology referral for at risk patients may be a way to minimise risk for end-stage renal disease or death.**

#### Introduction

Acute kidney injury (AKI) complicates around 20% of hospitalisations, and is associated with morbidity and mortality (Uchino et al. 2006; Wang et al. 2012). In-hospital mortality rates of more than 50% for patients on renal replacement therapy (RRT) are common (Hoste and Schurgers 2008). The most recent studies report lower, albeit still high, 90-day mortality rates: 34% for critically ill patients with AKI and 39% for the subgroup requiring RRT (Nisula et al. 2013).

With a focus on morbidity, a US study from 2012 demonstrated that only 8.5% of AKI survivors were referred to nephrologists and that severity of AKI did not affect referral rates (Siew et al. 2012). This ignores the fact that the recovery phase of AKI may represent the best opportunity to intervene in the negative outcomes of AKI (Chawla 2011). Most major cardiovascular events during a stay in hospital or in the intensive care unit (ICU) will trigger a cardiology referral. However, we as intensivists seem to lack knowledge regarding long-term kidney morbidity and/or fail to act in the best interest of our AKI survivors.

This review therefore details two post-ICU consequences for AKI survivors, namely chronic kidney disease (CKD) and end-stage renal disease (ESRD). More specifically, we seek to assess the risk factors associated with AKI survivors progressing to CKD/ESRD and to examine if interventions during the ICU stay may have an impact on long-term morbidity.

#### Co-morbidities or Intrinsic Factors Affecting Long-Term Outcome

The link between AKI and the development of CKD has been shown in numerous investigations. Heung and Chawla looked at dose-response, and showed that the risk of CKD, in over 20,000 cardiac surgery patients without pre-existing CKD, rose progressively with increasing rise in creatinine (Heung and Chawla 2012). These findings were supported by a recent meta-analysis: the risk of developing CKD rose with mild, moderate and severe AKI when compared with no AKI (adjusted HR 2.0, 3.3 and 28.2, respectively) (Coca et al. 2012). Moreover, in a Veterans Affairs database study of diabetic patients, Thakar et al. demonstrated how AKI patients, as compared to non-AKI patients, were significantly more likely to develop CKD stage 4 (HR 3.56, 95% CI 2.76-4.61). Interestingly, patients with multiple episodes of AKI had a more than twice-fold risk for CKD for each additional AKI hit (HR 2.02, 95% CI 1.78–2.30) (Thakar et al. 2011).

Looking at aggravating factors for patients in the ICU we see a number of non-surprising findings. Advanced age, presence of diabetes mellitus and decreased baseline estimated glomerular filtration rate have been identified as risk factors for the progression to advanced stage CKD in studies on AKI survivors (Amdur et al. 2009; Ishani et al. 2009; Lo et al. 2009; Wald et al. 2009). Adding to that panel of risks, a low serum albumin concentration is a strong predictor of poor long-term renal outcome (Chawla et al. 2011).

#### ICU Treatment

Besides the baseline risks detailed above, are there interventions when the patient is in the ICU that have an effect on the long-term outcome? Avoiding nephrotoxic agents if possible, considering alternatives to radio contrast procedures and ensuring adequate volume status and perfusion pressures are obvious steps to take. Having stated that, we acknowledge that the last part, "ensuring adequate volume status and perfusion pressures" are easy statements on paper but hard to gauge in the clinical reality in which we operate.

Interventions that we can try to analyse include: modality, timing and dose of renal replacement therapy (RRT). Furthermore, we can look into fluid removal management in AKI patients.

#### RRT Modality

If a patient needs RRT, multiple studies point to the fact that modality is important. In short, it seems that continuous renal replacement therapy (CRRT) holds a long-term outcome benefit over intermittent RRT (IRRT) in the ICU setting. A large systematic review and meta-analysis from 2013 identified 23 studies: seven randomised controlled trials (RCTs) and 16 observational studies involving 472 and 3,499 survivors respectively (Schneider et al. 2013). Pooling RCTs showed no difference in the rate of dialysis dependence among survivors (relative risk (RR) 1.15 [95 % CI 0.78–1.68]). However, pooled analyses of observational studies indicated a higher rate of dialysis dependence among survivors who initially received IRRT as compared with CRRT (RR 1.99 [95 % CI 1.53–2.59]).

#### Timing of RRT

When to start RRT has been the subject of debate. In the absence of life-threatening derangements associated with kidney failure (metabolic acidosis, hyperkalaemia, uraemia, and/or fluid overload), there is limited evidence toguide clinicians on when to initiate RRT in the critically ill patient with AKI. Some data suggest that earlier RRT initiation may attenuate kidney-specific and non-kidney organ injury from acidaemia, uraemia, fluid overload, and systemic inflammation (Clark et al. 2006; Matson et al. 2004). This could potentially translate into improved survival and earlier recovery of kidney function (Matson et al. 2004). A meta-analysis from the University of Alberta and the Harvard School of Public Health did shed some light on this issue (Karvellas et al. 2011): 15 unique studies (two randomised, four prospective cohort and nine retrospective cohort) were analysed, and early RRT initiation was associated with reduced mortality compared to late initiation (pooled OR 0.45; 95% CI, 0.28 to 0.72, $P < 0.001$). Five studies (of seven reporting data) described a higher rate of kidney recovery to dialysis independence at hospital discharge for patients receiving early RRT. Pooled analysis of these seven studies showed a non-significant summary estimate favouring early RRT (OR 0.62, 95% CI 0.34 to 1.13).

#### Dose of RRT

The RRT dose has not been shown to have an effect on mortality or the rate of renal recovery in the two large RCTs on the subject (VA/NIH Acute Renal Failure Trial Network 2008; RENAL Replacement Therapy Study Investigators 2009). However, please note that these studies did not detail fluid removal as a determinant of dose. Instead they viewed dose as an *a priori* determined level of high or low intensity, where patients could be treated both with IRRT and CRRT (VA/NIH Acute Renal Failure Trial Network 2008) or CRRT-only effluent flow based on body weight, either 40 ml/kg/h or 25 ml/kg/h (RENAL Replacement Therapy Study Investigators. 2009).

#### Fluid Management

As stated above, fluid therapy aiming to improve renal perfusion and oxygen delivery remains a cornerstone in the management of patients with, or at risk of, AKI. Current evidence suggests that early goal-directed correction of hypovolaemia with fluids improves renal outcome (Oliveira et al. 2008) and survival (Oliveira et al. 2008; Rivers et al, 2001) in septic patients. Evidence from observational studies, however, indicates that a prolonged and uncritical fluid therapy, causing fluid accumulation, might negatively impact recovery from AKI. The results from these studies highlight the importance of timing of RRT initiation as well as the delivered dose, not in terms of molecular clearance but rather measured as the extent of fluid removal.

Hayes and co-workers investigated 76 RRTtreated children in a paediatric ICU, focusing on the percentage fluid overload (%FO) at RRT initiation and outcome (Hayes et al. 2009). Forty-two children survived to hospital discharge, and these patients had significantly lower %FO (7.3%) at RRT initiation than non-survivors (22.3%). Although RRT was successfully discontinued in all survivors without preexisting ESRD and with complete follow-up data ($n = 37$), those with a %FO of >20% spent a longer time on the RRT machine as compared to children with a %FO of <20% (median 8 vs. 26 days, $p = 0.0038$).

Heung and co-workers found similar results when they studied 170 adult patients treated with RRT for AKI (Heung et al. 2012). The primary endpoint was recovery of adequate renal function to discontinue dialysis for atleast two weeks within one year after dialysis initiation. Thirty-six percent of patients met the renal recovery criterion. Renal recovery was highly associated with survival, as 71% of patients who met this criterion were alive at one year. In contrast, only 15% of patients who did not recover their renal function were alive at this time. Multivariate Cox proportional hazard modelling was used to identify variables independently associated with renalrecovery. A higher baseline serum creatinine, one or more major comorbidities, time between nephrology consultation and RRT initiation and use of vasopressors were all independently associated with a decreased likelihood of renal recovery. For fluid overload, each 1% increase in %FO at RRT initiation was associated with 3% decreased likelihood of renal recovery at one year.

In the study by Bouchard and colleagues, the effect of fluid overload on renal recovery was less consistent (Bouchard et al. 2009). Their study comprised 618 AKI patients from five academic centres in North America. Fluid overload was defined as a percentage of fluid accumulation >10% over baseline weight at hospital admission. Fluid overload at dialysis initiation was not related to dialysis independence at hospital discharge. Neither was fluid overload at AKI diagnosis associated with recovery of kidney function, as defined by a serum creatinine ≤44 μmol/l or ≤20% above baseline. Patients with fluid overload at the time of their peak creatinine were, however, significantly less likely to recover renal function than patients without fluid overload.

The importance of a negative fluid balance during RRT on mortality and renal recovery was recently highlighted in a post-hoc analysis of the data from the RENAL study (RENAL Replacement Therapy Study Investigators 2012). The authors showed not only that a negative mean daily fluid balance during RRT was associated with a nearly 70% reduction in 90-day risk of death, but also with more RRT-free days at day 90. These associations persisted after adjustment for numerous potential confounders using different statistical models.

Notably, continuous RRT was used in more than 90% of patients in the RENAL study. The superiority of continuous over intermittent RRT in achieving net fluid removal in critically ill AKI patients has been clearly demonstrated (Bouchard et al. 2009). The incapability of managing fluid balance with intermittent haemodialysis in critically ill patients is one likely explanation for the negative impact of this modality on renal recovery seen in previous studies (Bell et al. 2007).

#### Conclusions

AKI is associated with high mortality and long term outcomes like chronic kidney disease and end-stage renal disease. The outcomes are affected by intrinsic factors, such as age and comorbities, but the ICU management of these patients does play a role. Modality, dose and timing of RRT with a focus on early prevention of harmful fluid accumulation, and not only for clearance of waste products, may be important factors. For certain patients, a nephrology referral could lessen the risk of the transition from AKI via CKD to ESRD.

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