Promoting Kidney Function Recovery in Patients with AKI Requiring RRT

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Abstract
AKI requiring RRT is associated with high mortality, morbidity, and long-term consequences, including CKD and ESRD. Many patients never recover kidney function; in others, kidney function improves over a period of many weeks or months. Methodologic constraints of the available literature limit our understanding of the recovery process and hamper adequate intervention. Current management strategies have focused on acute care and short-term mortality, but new data indicate that long-term consequences of AKI requiring RRT are substantial. Promotion of kidney function recovery is a neglected focus of research and intervention. This lack of emphasis on recovery is illustrated by the relative paucity of research in this area and by the lack of demonstrated effective management strategies. In this article the epidemiologic implications of kidney recovery after AKI requiring RRT are discussed, the available literature and its methodologic constraints are reviewed, and strategies to improve the understanding of factors that affect kidney function recovery are proposed. Measures to promote kidney function recovery are a serious unmet need, with a great potential to improve short- and long-term patient outcomes.


Introduction
AKI requiring RRT (commonly designated AKI-D) is a common and serious condition with substantial morbidity, mortality, and associated CKD (1,2). The incidence of AKI-D in the United States is increasing; between 2000 and 2009, the number of new patients of AKI-D rose by 10% per year (3). Overall, AKI-D occurs in approximately 1%–2% of hospitalized patients and in 6%–7% of critically ill patients (4).

The mortality associated with AKI-D is high and is greater than other serious illnesses such as acute respiratory distress syndrome (5) or myocardial infarction (MI) (6). Overall in-hospital mortality of patients with AKI-D is 33% (7) and between 50% and 60% in the intensive care unit (ICU) (8,9). Survivors of AKI-D are at risk for long-term complications, including CKD (10–13), ESRD (2,14), bone fractures (15), upper gastrointestinal bleeding (16), stroke (17), and cardiovascular events, including MI and congestive heart failure (6,12). Because observational studies suggest that adverse outcomes are mitigated when the severity and duration of AKI is reduced (18,19), it is hypothesized that targeted measures to facilitate kidney function recovery might improve both kidney- and non-kidney-related outcomes. However, despite these potential benefits, clinical management guidelines focusing on kidney function recovery are scarce, and therapies to accelerate kidney function recovery are practically nonexistent. Investigation to identify effective management strategies and therapies that accelerate kidney function recovery in AKI is sorely needed.

In this review, we discuss the magnitude of the problem of kidney function recovery in patients with AKI-D (Figure 1); the known clinical factors and potential management strategies that may facilitate recovery; the priority areas of research on AKI-D management; and the effect of kidney function recovery on patient survival, quality of life, and cost. We submit that efforts to improve kidney function recovery in patients with AKI-D are a serious unmet need, with great potential to benefit patients.

Patients with AKI-D are particularly vulnerable to a lack of adequate outpatient dialysis options and an absence of well-defined clinical management strategies. Our accompanying article (20) discusses the policy implications of this problem and suggests practical management strategies for these patients.

Kidney Function Recovery and Long-Term Outcomes of Patients with AKI-D
Kidney function recovery of AKI-D has been best studied in the context of the short-term ICU stay. Dialysis independence at the time of hospital discharge is the most commonly reported outcome. Studies suggest that 10%–30% of survivors with AKI-D remain dialysis dependent at the time of hospital discharge (8,21–27). The largest epidemiologic study regarding outcomes of patients with AKI-D is the Beginning and Ending Supportive Therapy for the Kidney cohort (N=1006) (8). In this study, reporting the outcomes of critically ill patients treated with AKI requiring continuous RRT (CRRT) in 54 ICUs in 23 countries, 15% of survivors were dialysis dependent at hospital discharge. Continued dialysis dependence after hospital discharge and up to 90 days is variably reported, ranging from 16% to 29% (27,28). By arbitrary
convention, 90 days is an important time point because it is
the defined time when many patients are considered to
have reached ESRD.

Studies specifically examining the outcomes of outpatients
who still require dialysis at hospital discharge are lacking.
Better epidemiologic data are essential to inform patients
and providers regarding the potential for kidney function
recovery and to help determine when kidney function loss
might reasonably be considered irreversible.

Baseline kidney function is the most consistently identified
factor affecting kidney function recovery in patients with AKI-D
(27,29–32). Other factors shown to adversely affect kidney
function recovery include increasing age, diabetes mellitus,
heart failure, and increased number of comorbidities
(27,33,34).

To our knowledge, only one study has specifically ex-
amined the outcome of hospitalized patients with AKI-D
who were transferred to an outpatient dialysis facility (34).
At 6 months, the cumulative recovery rate was 21%. Within
6 months, whereas 50% of patients with AKI-D with baseline
eGFR>60 ml/min per 1.73 m² recovered, only 17% of AKI-
on-CKD 3–4 patients (baseline eGFR 15–60 ml/min per 1.73 m²)
and zero CKD 5 patients (baseline eGFR<15 ml/min per 1.73 m²)
recovered function. In multivariable analysis, higher baseline eGFR, acute tubular necrosis (ATN) from
sepsis or surgery, and absence of heart failure were independent
predictors of survival. Among those who recovered, 73% of the recovery occurred within the first 3 months of
dialysis initiation; thereafter, 21% recovered between 3 and 6
months and only 6% beyond 6 months.

The design and performance of quality epidemiologic
studies of patients with AKI-D are challenging. Studies as-
sessing kidney function outcomes must address two key fac-
tors: (1) the effect of hospital survival on the interpretation
of kidney function recovery, and (2) the definition of kidney
function recovery.
Hospital Survival of Patients with AKI-D

Because the mortality rate of patients with AKI-D is high, reporting outcomes only among survivors can be misleading. Patients discharged after an episode of AKI have a 40% risk of dying in the 2 years after the initial hospitalization (35). As shown in Table 1, in-hospital mortality rates are 45%–79%, and dialysis dependence at hospital discharge occurs in 5%–13% when all patients (survivors and nonsurvivors) are considered. Therefore, comparing outcomes of epidemiologic studies and clinical trials of AKI-D requires that kidney function outcomes be considered for all patients (survivors and nonsurvivors). Studies with apparent benefit on function recovery may be less convincing when the entire cohort of patients with AKI-D is considered.

Definition of Kidney Function Recovery

Recovery has traditionally been defined by dialysis independence at hospital discharge. Recent clinical trials have also examined long-term outcomes at 60 and 90 days after initiation of dialysis (9,36). Indeed, alive and dialysis free at 90 days is likely to become a relevant clinical end point in future trials. Although dialysis independence is clearly important, merely assessing dialysis independence ignores the significant proportion of patients that may develop CKD. Defining kidney function recovery independent of dialysis status is not without challenges, however. Definitions that rely on a return to baseline kidney function are problematic because baseline kidney function is often unknown. Moreover, recent studies highlight the inadequacies of serum creatinine as a marker of GFR and recovery in the critically ill, whereby the use of eGFR and serum creatinine overestimated kidney function recovery compared with measured creatinine clearance (37,38). The discrepancy may be explained by the effect of muscle mass loss associated with prolonged critical illness (27,28,38). Efforts to standardize definitions of kidney function recovery in AKI-D are ongoing and are a key consideration in future clinical trial design.

Long-Term Outcomes of Patients with AKI-D Who Become Dialysis Independent within 90 Days

Although alive and dialysis free at 90 days is clearly an important milestone, AKI-D survivors remain at risk for serious complications within the next 1–5 years (6,12,15–17,32). The risk of ESRD after AKI-D after early dialysis independence is substantial, ranging from 8% to 21% of survivors (12,39). A large cohort of 4383 patients with AKI-D who were dialysis free for >90 days was analyzed for risk of subsequent ESRD (defined as dialysis requirement for at least 90 days). Of these, 8% ($n=356$) developed ESRD after a median follow-up of 2.4 years; of note, 34% ($n=1475$) of the cohort died during the follow-up period. Risk factors for return to dialysis included preexisting CKD, hypertension, and comorbidities (39). In another large matched cohort study, 4869 patients with AKI-D who were alive and dialysis free at 30 days had a 2.4 higher adjusted risk of developing ESRD at a mean follow-up of 3 years compared with 4869 matched controls (12). In a third study, the risk for ESRD in 3769 survivors of AKI-D who were dialysis free for at least 30 days was compared with the risk of ESRD in 13,598 well-matched
hospital controls (40). Median follow-up was 3 years. ESRD occurred in 8.5% of AKI-D (n=322) and 3% of controls (n=403), with an adjusted hazard ratio (HR) of 3.23. Although it has been suggested that patients with AKI-D are more likely to develop ESRD if they have underlying CKD, in the same study (40), the adjusted risk for ESRD was highest (at 15.5) among patients with AKI-D without pre-existing CKD.

The increased risk of ESRD after episodes of AKI-D is not surprising: many patients with AKI-D develop new CKD (10,13) or have worsening of preexisting CKD (10–13). Therefore, in a single-center study of patients with normal baseline kidney function (serum creatinine 1.3 mg/dl) after 54 months of follow-up, approximately 80% of AKI-D survivors developed CKD stage 3 or higher (10).

The long-term consequences of AKI-D extend beyond the risk of CKD and ESRD (41). Two large studies have examined survival, cardiovascular events, and stroke after AKI-D using data from the Taiwan National Healthcare System. In the first study, a total of 17,106 patients with AKI-D were identified; 4869 AKI-D survivors who were alive and dialysis free at 30 days were matched with 4869 controls (12). After a mean follow-up of 3 years, the risk of mortality and coronary events, including MI, were significantly greater in AKI-D. Mortality was 57.4% versus 34.6% in those with and without AKI-D (adjusted HR, 1.67), and 6.1% of AKI-D survivors experienced coronary events compared with 3.6% of controls (adjusted HR, 1.42). In the second study, 4315 AKI-D survivors who were alive and dialysis free at 30 days were matched with controls. After a mean follow-up of 3 years, patients with AKI-D had a higher risk of stroke (adjusted HR, 1.25) and a higher severity of stroke events (17). Remarkably, AKI-D conferred a future risk of coronary events (12) or stroke (17) that was similar to the risk conferred by diabetes.

AKI exposure portends severe kidney and cardiovascular outcomes. Patients who experience a simultaneous acute MI and AKI are twice as likely to experience subsequent admissions for congestive heart failure compared with patients with MI alone (6). The potentiation is bidirectional: AKI and MI increase the chances of subsequent kidney dysfunction and cardiovascular disease, and when AKI complicates and MI occurs, there is significantly increased risk of later development of cardio renal syndrome (42). Measured in terms of mortality and major adverse cardiovascular events, AKI exposure is potentially worse than an isolated ST-elevation acute MI (6).

In summary, data from large cohorts suggest that approximately one of every 12 survivors of AKI-D who become dialysis independent will require long-term dialysis within 3–5 years (39,40). Increased risk of ESRD occurs regardless of baseline CKD status. Nephrology care within 90 days of dialysis independence is associated with improved long-term survival (43). Although definitive evidence of benefit is still lacking, we recommend that nephrology follow-up occur within at least 90 days of dialysis discontinuation (ideally, within a month). We also suggest that, in this high-risk population, nephrology care be continued to mitigate progression to CKD or ESRD; to properly prepare for long-term dialysis if necessary; and to anticipate preventive care for other long-term complications, such as cardiovascular events, including heart failure and stroke (6).

Management Factors Affecting Kidney Function Recovery

Although RRT is the mainstay of supportive care in AKI-D, its application can have untoward effects and contribute to prolongation of kidney failure or impede recovery (44). No single management strategy has been proven to promote kidney function recovery in patients with AKI-D. Evidence-based clinical guidelines are currently lacking. The lack of quality data in this area is concerning, and research inquiry in this area is urgently needed.

In the absence of data, current management strategies focus on avoidance of additional kidney injury by maintaining kidney perfusion, avoiding hypotension, and avoiding nephrotoxins and technique-related infection (44). There is great interest to determine if modifications in RRT modality, fluid management, timing, RRT dose, anticoagulation strategies, and dialysis membranes effect recovery.

Renal Replacement Modality

By far, the RRT modality has received the most attention as a potential modifier of kidney function recovery. CRRT is considered by some to be superior to intermittent hemodialysis (IHD). It is hypothesized that hypotensive episodes during dialysis contribute to decreased kidney perfusion and compromise recovery. CRRT might be associated with better recovery because it affords better hemodynamic stability and less risk of intradialytic hypotension than IHD (45). Several animal models have demonstrated loss of renal blood flow autoregulation in AKI (46–48) that exposes the kidneys to additional injury, and the hemodynamic changes induced by IHD (9,49,50) are clinically important (51–59) and could adversely affect recovery.

However, available data are inadequate to definitively recommend one modality over another. Studies suggest that patients treated with CRRT versus IHD may experience better kidney function recovery (22,44,60–65). In a recent cohort study (66) of critically ill patients, 2004 patients treated with CRRT were matched with 2004 patients treated with IHD. At 3 years, the risk of chronic dialysis (dialysis >90 days) was significantly lower among patients initially treated with CRRT. A recent systematic review (45) analyzed several modality trials. The pooled analysis of observational studies indicated that among survivors of AKI-D, initial treatment with IHD was associated with a higher rate of dialysis dependence. However, the pooled analysis of the randomized controlled trials showed no difference in the rate of dialysis dependence between the two modalities among survivors. The large imbalances in underlying risk and competing risk for mortality in observational trials make it impossible to conclude at this time whether any modality is able to provide a better kidney functional outcome (67,68). Clinical trials are needed to demonstrate clear benefit.

Fluid Overload

Initiation of dialysis to avoid fluid overload might have a beneficial effect on recovery. In a single-center, retrospective cohort study (69), initiation of dialysis before the development of fluid overload was associated with improved recovery (fluid overload defined as ≥10% increase in baseline weight; recovery defined as dialysis independence at
In another study, dialysis initiation at >20% fluid overload was associated with prolonged time to kidney function recovery (70). Fluid overload might delay recovery because of (1) increased kidney edema and altered kidney architecture, (2) reduced kidney perfusion from increased intra-abdominal pressure, and (3) more aggressive fluid removal at dialysis initiation resulting in more intradialytic hypotension (69). Fluid overload at dialysis initiation is also associated with increased mortality (71–74). These studies are all observational and potentially affected by confounding; a causal link has not been established. Prospective interventional studies are needed to determine if fluid overload is merely a marker of severity of illness causing poor outcomes or whether preventing fluid overload (e.g., by early dialysis initiation) might improve outcomes.

**Dialysis Timing**

The optimal timing and indication of dialysis that confers kidney function benefit are unknown. Two systematic reviews on timing of dialysis initiation noted nonsignificant trends toward lower dialysis dependence with earlier initiation of dialysis (75,76). However, these systematic reviews pooled studies that defined timing of initiation on the basis of variable criteria, including levels of BUN and creatinine and duration of ICU stay; therefore, the results should be interpreted with caution.

**Dialysis Dose**

Increasing the dose of dialysis does not seem to affect kidney function recovery (77). In the ATN (78) and Intensity of continuous Renal Replacement Therapy in Critically Ill Patients (36) trials, there was no correlation between the intensity of dialysis and kidney function recovery. Furthermore, a meta-analysis on the effects of intensity of dialysis in eight trials including 3841 patients demonstrated no benefit of increased dialysis dose on kidney function recovery (79).

**Dialysis Membrane**

Aside from solute clearance, the interactions between blood and the dialysis membrane have been referred to as biocompatibility. A number of experimental studies in animal models suggested that complement and granulocyte activation during IHD could contribute to prolongation of AKI. Subsequent human prospective randomized trials in the 1990s suggested faster kidney function recovery and lower morbidity and mortality using biocompatible membranes (80–83), but more recent systematic reviews (44,84) showed no clinical benefit of biocompatible compared with less biocompatible membranes on kidney function recovery in patients with AKI-D receiving IHD. No published studies on the effects of membrane characteristics on recovery have been performed in patients receiving CRRT.

**Anticoagulation**

Although most of the studies on citrate anticoagulation are too small to evaluate patient outcome (85), the largest single-center trial (86) showed an increase in 3-month patient survival and a trend toward better kidney recovery, a benefit not explained by lesser bleeding. Anti-inflammatory effects of citrate may play a role in these preliminary results (87). These findings will require confirmation in larger multicenter trials.

**Kidney Function and Long-Term Outcomes of Patients with AKI-D Who Remain Dialysis Dependent beyond 90 Days**

Data suggest that dialysis dependence beyond 90 days is not uncommon in AKI-D: those patients are generally considered to have ESRD. In a cohort of 240 ICU patients with AKI-D, 22% of survivors (n = 19) were RRT-dependent at 1 year; notably, at 1 year, only 28% of the cohort (n = 68) were alive and free of dialysis (27). In another report of 1095 patients with AKI-D and normal baseline kidney function followed for 5 years, at 90 days 60% of patients survived and 17% of survivors (n = 107) still required dialysis and were considered ESRD. Of these, only six patients were eventually able to discontinue dialysis. Overall, the 5-year survival was significantly worse for patients with ESRD from AKI (41%) versus patients with nondiabetic kidney diseases as the cause of ESRD (61%); the cause of death was related to the cause of AKI in most patients (28).

In patients with AKI-D who are considered to have ESRD, kidney function recovery has been reported to occur in approximately 1%-2% of patients (88). Recently, however, among the 194,007 patients in the Medicare ESRD program identified via submission of Centers for Medicare and Medicaid Services 2728 forms between 2008 and 2009 (89), function recovery (defined as dialysis independence >1 year) occurred in 5.6% and 5.9% of patients in 2008 and 2009, respectively. Among these patients ATN alone accounted for 19.9% of all patients of renal recovery and 22% of those with sustained recovery. Among patients who were able to discontinue dialysis, most did so within the first 3 months: 69% for the entire cohort, and 81% for patients with a diagnosis of ATN. Although AKI (acute interstitial nephritis and ATN in particular) was the most common diagnosis associated with dialysis independence, dialysis independence was still higher than previous reports when diagnoses associated with AKI were excluded (i.e., 4.2% for 2008, 4.4% for 2009). Renal recovery was most likely to occur in the first month after incident hemodialysis; more than half of the patients of recovery occurred within the first 2 months, and more than two thirds occurred in the first 3 months of ESRD registration. Rate of recovery was fastest for patients with ATN as the primary cause of failure (89).

Because patients with AKI as the cause of ESRD have the highest rate of recovery of all patients with ESRD, we recommend that these patients be systematically monitored for kidney recovery during the first year of dialysis therapy. Indeed, methods to assess function recovery could reasonably be put in place for all patients initiating dialysis, as has been suggested by others (88), because approximately one in 20 of all patients with ESRD (AKI or non-AKI related) will achieve dialysis independence during the first year of dialysis initiation. Because most patients with ESRD who recover kidney function do so within the first 3 months of dialysis initiation, attention to recovery is especially important during this time period.

The most appropriate method to monitor kidney function recovery in the outpatient dialysis setting is still uncertain.
Studies suggest that in hospitalized patients, increased urine output is the most reliable early indicator of recovery (90). Falling serum creatinine is another well-recognized indicator of recovery; however, declining serum creatinine values might reflect catabolism, declining muscle mass, and malnutrition. Normalization of serum electrolytes, such as potassium and phosphorus, may also occur. In the ATN trial (9), dialysis was discontinued when the 6-hour creatinine clearance was >20 ml/min, but the most appropriate threshold for discontinuation is still uncertain (88). In the outpatient setting, a 24-hour urine collection for urea and creatinine is commonly used to calculate residual GFR. This method has been examined in intermittent hemodialysis patients and shown to be as accurate as inulin clearance (91). Unfortunately, symptoms and signs of recovery are nonspecific (Table 2), but they should still be assessed and considered for their potential value as early indicators. Those symptoms of recovery may also be conflicting; although some patients may develop an improved sense of well-being, other patients may begin to feel worse because of unnecessary fluid removal after gaining true body weight (88).

There are no guidelines on the proper methods to taper or discontinue dialysis in patients with AKI-D. Tapering of the dialysis by reducing time and frequency (88) or temporary discontinuation of dialysis with close monitoring may be appropriate. Whether dialysis is weaned or a trial of discontinuation is attempted, careful attention to medication dosing is warranted: some medications will need a higher dose (to account for recovering kidney function), but some will need a dose decrease (to account for the lack of dialysis removal). Phosphorus binders may also need adjustment to avoid hypophosphatemia in the face of recovering kidney function.

In addition to monitoring recovery, we propose measures to promote recovery, especially during the first 3 months postdialysis initiation. Specifically, intradialytic hypotension should be avoided, and for patients without symptomatic fluid overload, it may be advisable to delay establishing a dry weight until the patient has been deemed to have irreversible ESRD. Predialysis and home BP measurements must be carefully monitored, and BP medications must be carefully titrated to avoid hypotension. Readers are referred to extensive recent reviews on the subject of intradialytic hypotension and its management (92–96). Nephrotoxic medications and intravenous radiocontrast media should be avoided if possible.

Because most patients with ESRD will not recover function, we suggest that other management aspects of ESRD care be used as usual, regarding bone mineral management, anemia management, and permanent hemo- or peritoneal dialysis access creation. Patients with nonrecovering AKI must be offered the opportunity to explore all dialytic options as afforded to patients with progressive CKD. Although observational studies have suggested better preservation of residual function with peritoneal dialysis, other studies have failed to demonstrate a relationship (97) or are affected by confounding (88), and prospective randomized trials are not available.

For patients with AKI-D, the benefits of recognition and promotion of recovery in the outpatient setting cannot be overstated. Achievement of dialysis independence has substantial benefit in terms of improved quality of life and reduced morbidity. Measures to improve recovery will also reduce incident ESRD and its multiple, severe, long-term complications. Moreover, minimizing incident ESRD will have a substantial cost benefit, given the heavy health care expenditures associated with long-term care of patients with ESRD and their related complications.

Development of new measures able to predict recovery in patients with AKI-D would be greatly beneficial. Clinical prediction markers (e.g., baseline CKD, chronic heart failure, age, AKI phenotype) or novel biomarkers (68,98–102) may soon help identify individuals likely to recover and enable appropriate clinical trial enrollment and intensive monitoring of recovery.

Conclusions

AKI-D has traditionally been considered a problem of acute care management focused on hospital survival, but minimal attention has been paid to measures to promote kidney function recovery. We suggest that measures to recognize and promote recovery will potentially benefit both the increasingly incident patients with AKI-D and the overall health care system. Further, we suggest that the strategies with the most potential effect include the following: (1) implementation of improvements in the transition-of-care process after hospital discharge (as discussed in the accompanying Heung et al. [20]); (2) research in nondialytic interventions that promote recovery; (3) research in RRT innovations that promote recovery and avoid further kidney damage; (4) systematic monitoring of recovery in the outpatient setting for patients with persistent AKI, and for patients declared ESRD after AKI; and (5) research to identify clinical and biomarker predictors of recovery. Such measures will have significant benefits by reducing the very high morbidity and mortality currently associated with ESRD and providing a meaningful improvement in overall quality of life to patients with severe AKI.

Acknowledgments


Disclosures

None.

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