Acute Kidney Injury Leading to Chronic Kidney Disease and Long-Term Outcomes of Acute Kidney Injury: The Best Opportunity to Mitigate Acute Kidney Injury?

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Abstract
Acute kidney injury (AKI) has been shown to be associated with progression to chronic kidney disease (CKD). Multiple studies have shown that subsets of AKI survivors are at high risk for progression to advanced stage CKD and death. Risk factors associated with AKI survivors progressing to CKD have been identified and include advanced age, diabetes mellitus, decreased baseline glomerular filtration rate, severity of AKI and a low concentration of serum albumin. These risk factors can be utilized to identify those patients at highest risk for progression. Because progression to CKD in these AKI survivors typically occurs months after the initial AKI insult, a common injury pathway of CKD progression is probable, and therapeutic interventions that have been shown to retard CKD progression are likely to be effective in patients who survive AKI and then progress to CKD. AKI has many negative impacts across the spectrum of the disease. The 30-day mortality for patients with AKI is high, hence the preference to target AKI during the initiation phase. However, this phase is the most difficult point to treat AKI. The maintenance phase of AKI is longer in duration in comparison to the initiation phase, and thus the logistics are more amenable to study. However, the mainstay of treatment for the maintenance phase of AKI (renal replacement therapy) has been tested extensively and increasing the dose of renal replacement therapy has not been shown to improve outcome. Therefore, the recovery phase of AKI may represent the best opportunity to intervene in the negative outcomes of AKI.
Acute kidney injury (AKI) is becoming increasingly common in critically ill patients, and those patients with the most severe form of AKI requiring renal replacement therapy (RRT) have a mortality of 50–80% [1]. Over the past 10 years, there has been substantial progress in the field of AKI. In particular, consensus definitions, AKI biomarkers and the appropriate dosing of RRT have been established. Despite these advances, no drug or other therapeutic intervention currently exists for the treatment of AKI [2].

AKI is a clinical syndrome with a multitude of causes, which contributes to the complexities in designing therapies [3]. In addition, AKI has distinctive phases of injury (initiation, maintenance and recovery) [4]. While the consensus definition of AKI (RIFLE/AKIN) does not factor in the cause of AKI, it is likely that successful treatments for AKI will need to address the pathophysiologic mechanism of injury, particularly during the initiation phase [4].

AKI has been shown to be associated with progression to CKD [5–7]. Multiple studies assessing various cohorts of patients have shown that subsets of AKI survivors are at high risk for progression to advanced stage CKD [5–8]. In these studies, subsets of AKI survivors recovered renal function and then progressed to advanced stage CKD. Because the progression to CKD in these AKI survivors typically occurred months after the initial AKI insult, a common injury pathway of CKD progression is more probable, and therapeutic interventions that have been shown to forestall CKD progression are likely to be effective in patients who survive AKI and then progress to CKD.

Assessing the current landscape of AKI has shown that it has many negative impacts across the spectrum of the disease. Because the 30-day mortality for patients with AKI is 50–80%, there is an obvious desire to target AKI during the initiation phase [1]. However, this phase is the most difficult point to treat AKI. Despite the current progress in AKI biomarkers, real-time point-of-care tests for study intervention are not routinely available, except for a few select academic centers. The time window for intervention during the AKI initiation phase is short, and since these patients often cannot provide consent for themselves, the logistics of conducting these studies are daunting. These obstacles are further exacerbated by the fact that the understanding of the pathophysiologic mechanisms for the most common cause of AKI (sepsis-associated AKI, which contributes to half of all cases) is wanting [1, 9]. Moreover, the associated acute phase mortality of AKI is difficult to dissociate from the underlying disease.

The maintenance phase of AKI is longer in duration in comparison to the initiation phase, and thus the logistics are more amenable to study. However, the mainstay of treatment for the maintenance phase of AKI is RRT, which has been tested extensively. Two large well-powered prospective trials have shown that increasing the dose of RRT does not improve outcomes [10, 11]. Therefore, the
recovery phase of AKI may represent the best opportunity to intervene in the negative outcomes of AKI.

**Acute Kidney Injury as a Cause of Chronic Kidney Disease**

Prior to the era of CKD staging, it was generally accepted that patients who recovered from AKI had ‘good’ renal outcomes as assessed by a low incidence of end-stage renal disease (ESRD) [12]. These previous long-term studies were hampered by different definitions, variable follow-up times, and low overall numbers. More recently, from 2008 through 2010 (table 1), multiple studies assessing unique cohorts of patients demonstrated that patients who survive an episode of AKI have a significant risk for the development of advanced CKD (stage 4/5) [5–8].

Ishani et al. [6] assessed a random sample of Medicare beneficiaries and found that patients who had suffered an episode of AKI were more likely to develop ESRD than patients who did not have a history of AKI or CKD. In their analysis, the risk of ESRD was thirteen times higher than patients without a history of AKI or CKD. Because this study utilized diagnostic codes, it is difficult to determine the proportion of patients who suffered AKI and then progressed directly to ESRD as compared to patients who suffered AKI, recovered renal function and then progressed to ESRD [6]. Lo et al. [7], utilizing a database from the health insurer Kaiser Permanente, retrospectively studied inpatient admissions. Patients who suffered AKI (dialysis-requiring episode of AKI) were compared to patients who did not suffer an episode of AKI. Patients with a history of

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Key findings</th>
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<tbody>
<tr>
<td>Ali [26] 2007</td>
<td>562</td>
<td>AKI-F → 51% recover full renal function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ACRF-F → 28% recover full renal function</td>
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<tr>
<td>Ishani [6] 2009</td>
<td>233,803</td>
<td>AKI → 13 times more likely to develop ESRD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ACRF → 41 times more likely to develop ESRD</td>
</tr>
<tr>
<td>Hsu [28] 2009</td>
<td>1061</td>
<td>ACRF-F → 42–63% of hospital survivors progressed to ESRD</td>
</tr>
<tr>
<td>Lo [7] 2009</td>
<td>703</td>
<td>AKI-F survivors are 28 times more likely to develop advanced CKD</td>
</tr>
<tr>
<td>Amdur [5] 2009</td>
<td>5,404</td>
<td>20% of patients with a diagnosis of ATN progress to CKD4 within 20 months</td>
</tr>
<tr>
<td>Wald [8] 2009</td>
<td>3,769</td>
<td>AKI-F survivors are 3 times more likely to develop ESRD</td>
</tr>
</tbody>
</table>

AKI-F = Acute kidney injury RIFLE F; ACRF = acute chronic renal failure; ATN = acute tubular necrosis.
ESRD or a pre-admission estimated glomerular filtration rate <45 ml/min/1.73 m² were excluded. In this study, the investigators found that an episode of dialysis requiring AKI was associated with a 28-fold increase of developing advanced CKD and a twofold increase in mortality. Because patients who developed ESRD within 30 days of discharge were excluded from the long-term follow-up of advanced CKD, these data are consistent with a severe form of AKI followed by renal recovery and then progression to advanced stage CKD [7]. Wald et al. [8] conducted a population-based cohort study of patients in Ontario, Canada with AKI patients who required in-hospital dialysis and survived free of dialysis for at least 30 days after discharge. These patients were matched with patients without AKI or dialysis during their index hospitalization. Patients with AKI requiring dialysis were over three times more likely to develop ESRD as compared to controlled matched patients.

We assessed a United States Department of Veterans Affairs database to ascertain long-term renal function in over 79,000 hospitalized patients [5]. Within this cohort, 63,491 patients were hospitalized for acute myocardial infarction or pneumonia without AKI and designated as controls. Another 5,404 hospitalized patients, which comprised the AKI group, had diagnostic codes indicating acute renal failure or acute tubular necrosis. Over the 5-year follow-up period, renal function deteriorated over time in all groups, but with significantly greater severity in those who had acute renal failure and acute tubular necrosis compared to controls. Patients with AKI, especially those with acute tubular necrosis, were more likely than controls to enter stage 4/5 CKD. We found that patients who had an episode of AKI were at high risk for the development of stage 4 disease and had a reduced survival time when compared to control patients [5].

In aggregate, these studies underscore the strong association between AKI and the future development of CKD.

Identification of Patients and Risk Factors for Chronic Kidney Disease Progression

The above studies in AKI survivors identified advanced age, presence of diabetes mellitus and decreased baseline estimated glomerular filtration rate as risk factors for the progression to advanced stage CKD. More recently, severity of AKI has been linked to CKD progression in survivors of AKI. Ishani et al. [13] assessed patients who underwent cardiac surgery and found that the magnitude of serum creatinine during the postoperative hospital course was directly linked to progression. This effect was seen in patients with de novo AKI as well as in patients with acute on chronic renal failure [13]. Similarly, we have recently shown that in addition to severity of AKI, a low serum albumin concentration is a strong predictor of poor long-term renal outcome [14]. The strong predictive value of serum albumin levels as a predictor of CKD progression is not
surprising because low albumin levels have been associated with poor outcomes in a variety of diseases including ESRD, surgical illness and acute stroke [15–17]. Low levels of serum albumin can be due to either nutrition-related factors and/or high levels of inflammation [18]. Given that multiple studies have linked inflammation to AKI, it is likely that the predictive value of low concentrations of serum albumin to CKD progression is a composite measure of increased inflammation [19–21].

We assessed a cohort of patients with a spectrum of AKI from RIFLE stages R through F, and showed that the severity of AKI is associated with progression to advanced CKD (fig. 1). In particular, we showed that patients who require dialysis are at much higher risk for progression to CKD than patients with less severe AKI. The precise mechanism by which AKI causes CKD is unknown. Preclinical studies suggest several potential mechanisms for how AKI can cause CKD: acute endothelial injury leading to vascular dropout, nephron loss followed by glomerular hypertrophy or development of fibrosis after sustaining AKI [22, 23].

In order to help clinicians identify AKI survivors at high-risk for CKD progression, we developed three multivariable models. The most accessible model is based on sentinel clinical events (RIFLE stage, need for dialysis, etc.) [14]. This model performed well with 11% of the CKD variance explained (area under ROC curve = 0.77). We validated this equation in a separate large cohort of hospitalized veterans which resulted in p < 0.001 and c-statistics ≥0.81, signifying good reproducibility. Because these endpoints are accessible, clinicians could potentially use this equation to risk stratify AKI survivors who are at the highest risk for progression to CKD [14].

Interventions during the Recovery Phase of Acute Kidney Injury

Because a primary care provider sees most AKI patients following an AKI episode, these patients are accessible for intervention. At 30 days after AKI discharge, 74.5% have seen a primary physician compared to 11.9 and 29.5%, respectively, who see a nephrologist or cardiologist [24]. Surprisingly, only about one third of AKI patients who suffer AKI requiring dialysis see a nephrologist within 30 days of discharge. This increases to 48.6% within 1 year of discharge, which is likely a result of rising serum creatinine [24]. Overall, a very small fraction of AKI patients are currently followed by a nephrologist after an AKI discharge [24]. To put this into context, an assessment of the nephrology follow-up of AKI survivors as compared to the cardiology follow-up of myocardial infarction survivors reveals a stark difference (11.9 vs. 76%, respectively) [24, 25].

The public health impact of the long-term outcomes of AKI is significant. The population incidence of AKI is approximately 2,100 pmp [26]. Given
Fig. 1. Patients who were still alive ≥1 year after index hospitalization. a Time vs. mean estimated glomerular filtration rate (eGFR) in AKI survivors [14]. b Time vs. mean serum creatinine (SC) in AKI survivors [14].
the population of the developed world (USA, Canada, Western Europe and Australia) of approximately 1 billion, this means that there will be over 2 million cases of AKI this year, with an expected 1.5 million AKI survivors. Of these patients, approximately 15–20% will progress to advanced stage CKD within 24 months, resulting in approximately 300,000–400,000 cases of advanced CKD per year. Given the increasing incidence of AKI in the aging population [27], the numbers above are expected to increase.

In our view, the first interventional study to mitigate the progression of CKD in AKI survivors should include testing the standard approach that is currently used to treat CKD patients: blood pressure control, nephrotoxin avoidance and nutritional intervention. A potential study design would use a risk factor risk score to identify the patients at highest risk for CKD progression. Those patients would then be enrolled into a clinical trial during their index hospitalization of AKI. Patients would be randomized to one of three interventions: intervention 1, standard primary care follow-up at scheduled visits; intervention 2, standard primary care follow-up, with scheduled nephrology follow-up for blood pressure control, nutritional intervention for sodium and protein diet counseling, and nephrotoxin avoidance education; and intervention 3, interventions 1 and 2, plus renin-angiotensin-aldosterone system blockade. Other interventions that could be added or substituted in the above example include HMG Co-A reductase inhibitors, and antiproliferative agents.

Conclusions

Patients with AKI suffer a high short-term mortality rate and subsets of those patients who survive are at increased risk for developing CKD. Interventions targeted during the initiation phase of AKI are the most desirable. However, the inadequate understanding of the pathophysiologic mechanisms of this phase of AKI in combination with a paucity of candidate therapeutic agents underlies the complexities of bringing a successful intervention from the bench to the bedside.

While the recovery phase of AKI may be less appealing as a point to intervene because of the associated high short-term mortality of AKI, the advantages of intervening in the recovery phase of AKI are numerous. The mechanism of CKD progression is more remote to the initial AKI. Patients at risk can be identified. The pathophysiology of CKD progression is well understood, and similarities between CKD progression and AKI progression to CKD are likely. The time to progression from AKI to recovery to advanced stage CKD occurs over months. Because of this longer timeline, incremental dose titration of potential therapeutic agents can be done more effectively, thereby potentially decreasing adverse events. Further, AKI survivors currently have no standard of care intervention, and modest interventions could have significant effects.
In short, intervention at the recovery stage of AKI possesses the important prerequisites for a successful intervention and this should be a focus for the AKI research community.

References


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